(FILE 'HOME' ENTERED AT 15:54:07 ON 10 JUL 2003)

FILE 'USPATFULL, EMBASE, SCISEARCH, CAPLUS, JAPIO' ENTERED AT 15:59:05 ON 10 JUL 2003

ACTIVAT L10046575/L

L1 (1) SEA FILE=REGISTRY ABB=ON PLU=ON TINIDAZOLE/CN
L2 (662) SEA FILE=CAPLUS ABB=ON PLU=ON L1
L3 (211) SEA FILE=CAPLUS ABB=ON PLU=ON L1/USES
L4 (13) SEA FILE=CAPLUS ABB=ON PLU=ON L3 AND (SKIN)
L5 (200) SEA FILE=USPATFULL ABB=ON PLU=ON TINIDAZOLE OR L1 OR FASIGIN
L6 (74) SEA FILE=USPATFULL ABB=ON PLU=ON L5 AND TREAT? AND SKIN
L7 (34) SEA FILE=USPATFULL ABB=ON PLU=ON L6 AND DERMAT?

L8 196 FILE USPATFULL
L9 2507 FILE EMBASE
L10 604 FILE SCISEARCH
L11 651 FILE CAPLUS
L12 7 FILE JAPIO
TOTAL FOR ALL FILES
L13 3965 S L5
L14 4129 FILE USPATFULL
L15 8745 FILE EMBASE
L16 6728 FILE SCISEARCH
L17 2426 FILE CAPLUS
L18 512 FILE JAPIO
TOTAL FOR ALL FILES
L19 22540 S ATOPIC DERMATITIS
L20 4232 FILE USPATFULL
L21 8836 FILE EMBASE
L22 6810 FILE SCISEARCH
L23 3273 FILE CAPLUS
L24 519 FILE JAPIO
TOTAL FOR ALL FILES
L25 23670 S ATOPIC (5A) DERMATITIS
L26 1139 FILE USPATFULL
L27 251 FILE EMBASE
L28 135 FILE SCISEARCH
L29 220 FILE CAPLUS
L30 9 FILE JAPIO
TOTAL FOR ALL FILES
L31 1754 S L25 AND IMMUNOSUPP?
L32 46 FILE USPATFULL
L33 17 FILE EMBASE
L34 1 FILE SCISEARCH
L35 4 FILE CAPLUS
L36 0 FILE JAPIO
TOTAL FOR ALL FILES
L37 68 S L13 AND IMMUNOSUPP?
L38 3 FILE USPATFULL
L39 1 FILE EMBASE
L40 1 FILE SCISEARCH
L41 1 FILE CAPLUS
L42 0 FILE JAPIO
TOTAL FOR ALL FILES
L43 6 S L31 AND L37
L44 3 FILE USPATFULL
L45 1 FILE EMBASE
L46 1 FILE SCISEARCH
L47 1 FILE CAPLUS
L48 0 FILE JAPIO
TOTAL FOR ALL FILES
L49 6 S L31 AND L13

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L50             2 FILE USPATFULL
L51             2 FILE EMBASE
L52             1 FILE SCISEARCH
L53             3 FILE CAPLUS
L54             0 FILE JAPIO
     TOTAL FOR ALL FILES
L55             8 S L13 (2S) IMMUNOSUPP?
L56           367 FILE USPATFULL
L57           177 FILE EMBASE
L58            33 FILE SCISEARCH
L59            27 FILE CAPLUS
L60             1 FILE JAPIO
     TOTAL FOR ALL FILES
L61           605 S METRONIDAZOLE AND (DERMATITIS)
L62            13 FILE USPATFULL
L63            11 FILE EMBASE
L64             2 FILE SCISEARCH
L65             4 FILE CAPLUS
L66             2 FILE JAPIO
     TOTAL FOR ALL FILES
L67            32 S L13 AND (DERMATITIS)
L68             1 FILE USPATFULL
L69             3 FILE EMBASE
L70             2 FILE SCISEARCH
L71             1 FILE CAPLUS
L72             1 FILE JAPIO
     TOTAL FOR ALL FILES
L73             8 S L13 (2S) (DERMATITIS)
L74            11 FILE USPATFULL
L75            29 FILE EMBASE
L76            12 FILE SCISEARCH
L77             8 FILE CAPLUS
L78             1 FILE JAPIO
     TOTAL FOR ALL FILES
L79            61 S METRONIDAZOLE (1S) (DERMATITIS) (1S) TREAT?
L80            46 FILE USPATFULL
L81             5 FILE EMBASE
L82             3 FILE SCISEARCH
L83             6 FILE CAPLUS
L84             4 FILE JAPIO
     TOTAL FOR ALL FILES
L85            64 S NITROIMIDAZOLE AND DERMATITIS
L86            14 FILE USPATFULL
L87             2 FILE EMBASE
L88             1 FILE SCISEARCH
L89             2 FILE CAPLUS
L90             3 FILE JAPIO
     TOTAL FOR ALL FILES
L91            22 S NITROIMIDAZOLE AND DERMATITIS AND ATOPIC

=> d 15-19 all
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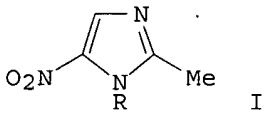
L85 ANSWER 60 OF 64 CAPLUS COPYRIGHT 2003 ACS
AN 1994:14914 CAPLUS
DN 120:14914
TI **Nitroimidazoles** for the treatment of inflammatory and infectious skin disorders
IN Sjoelund, Eilert
PA Hydro Pharma Sverige AB, Swed.
SO PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-415
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9320817	A1	19931028	WO 1993-SE276	19930331
	W: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	SE 9201188	A	19931015	SE 1992-1188	19920414
	SE 506509	C2	19971222		
	AU 9339640	A1	19931118	AU 1993-39640	19930331
PRAI	SE 1992-1188		19920414		
	WO 1993-SE276		19930331		

OS MARPAT 120:14914
GI



I

AB Topical formulations contg. **nitroimidazoles** [I; R = (CH2)mSO2(CH2)nMe, (CH2)mSO2CHMe2; m = 2,3; n = 0,1] are effective for the treatment of inflammatory and infectious skin disorders, e.g. eczema, acne, and rosacea. A cream contg. 2% tinidazole was formulated and tested on acne patients.

ST topical **nitroimidazole** infectious inflammatory skin disease; cream tinidazole acne treatment

IT Acne
Dermatitis
(treatment of, topical prepns. contg. **nitroimidazoles** for)

IT Pharmaceutical dosage forms
(emulsions, topical, **nitroimidazoles** in, for treatment of inflammatory and infectious skin disorders)

IT Pharmaceutical dosage forms
(gels, topical, **nitroimidazoles** in, for treatment of inflammatory and infectious skin disorders)

IT Skin, disease
(infection, treatment of, topical prepns. contg. **nitroimidazoles** for)

IT Pharmaceutical dosage forms
(ointments, creams, **nitroimidazoles** in, for treatment of inflammatory and infectious skin disorders)

IT Skin, disease
(rosacea, treatment of, topical prepns. contg. **nitroimidazoles** for)

IT Pharmaceutical dosage forms

(topical, **nitroimidazoles** in, for treatment of inflammatory and infectious skin disorders)

IT 19387-91-8, Tinidazole
RL: BIOL (Biological study)
(inflammatory and infectious skin disorders treatment with)

L85 ANSWER 59 OF 64 CAPLUS COPYRIGHT 2003 ACS
AN 1997:142224 CAPLUS
DN 126:190233
TI Occupational allergic contact **dermatitis** from 5-chloro-1-methyl-4-**nitroimidazole**
AU Jolanki, Riitta; Alanko, Kristiina; Pfaffli, Pirkko; Estlander, Tuula; Kanerva, Lasse
CS Department of Occupational Medicine, Finnish Institute of Occupational Health (FIOH), Helsinki, FIN-00250, Finland
SO Contact Dermatitis (1997), 36(1), 53-54
CODEN: CODEDG; ISSN: 0105-1873
PB Munksgaard
DT Journal
LA English
CC 59-5 (Air Pollution and Industrial Hygiene)
Section cross-reference(s): 4, 63
AB A 46-yr old man, working on azathioprine synthesis, developed a rash on the face, esp. the eyelids, neck, and hands, after minimal exposure to the drug intermediate, AZA III, in powder form, when he weighed the chem. in small amts. without using protective gloves. This contact allergy to 5-chloro-1-methyl-4-**nitroimidazole**, an intermediate product of azathioprine, had not been previously reported. This compd. was shown to be present in the end products, azathioprine and azathioprine tablets, in amts. sufficient to induce allergic patch test reactions in a sensitized patient. Cross-reactivity was found between 5-chloro-1-methyl-4-**nitroimidazole** and 3 of 6 imidazole derivs. used as antifungal drugs tested.
ST occupational health hazard azathioprine manufg; allergic contact **dermatitis** occupational exposure azathioprine; chloromethyl **nitroimidazole** exposure allergic contact **dermatitis**
IT Industrial hygiene
Occupational health hazard
(allergic contact **dermatitis** from occupational exposure to 5-chloro-1-methyl-4-**nitroimidazole** during azathioprine manufg. and handling)
IT **Dermatitis**
(allergic, contact; allergic contact **dermatitis** from occupational exposure to 5-chloro-1-methyl-4-**nitroimidazole** during azathioprine manufg. and handling)
IT Drugs
(anti-fungal; allergic contact **dermatitis** from occupational exposure to 5-chloro-1-methyl-4-**nitroimidazole** during azathioprine manufg. and handling)
IT 288-32-4DP, Imidazole, derivs. 446-86-6P, Azathioprine
RL: ADV (Adverse effect, including toxicity); IMF (Industrial manufacture); TEM (Technical or engineered material use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(allergic contact **dermatitis** from occupational exposure to 5-chloro-1-methyl-4-**nitroimidazole** during azathioprine manufg. and handling)
IT 4897-25-0, 5-Chloro-1-methyl-4-**nitroimidazole**
RL: ADV (Adverse effect, including toxicity); TEM (Technical or engineered material use); BIOL (Biological study); USES (Uses)
(allergic contact **dermatitis** from occupational exposure to 5-chloro-1-methyl-4-**nitroimidazole** during azathioprine manufg. and handling)

8906537 A1 1989 CAPLUS

L85 ANSWER 57 OF 64 CAPLUS COPYRIGHT 2003 ACS
AN 2000:868107 CAPLUS
DN 134:75349
TI Occupational contact **dermatitis**: New allergens
AU Kanerva, L.; Estlander, T.; Jolanki, R.; Alanko, K.
CS Section of Dermatology, Finnish Institute of Occupational Health, Helsinki, Finland
SO Dermatology at the Millennium, The Proceedings of the World Congress of Dermatology, 19th, Sydney, Australia, June 15-20, 1997 (1999), Meeting Date 1997, 224-228. Editor(s): Dyall-Smith, Delwyn; Marks, Robin. Publisher: Parthenon Publishing Group, Pearl River, N. Y.
CODEN: 69ARYA
DT Conference; General Review
LA English
CC 59-0 (Air Pollution and Industrial Hygiene)
Section cross-reference(s): 4
AB A review with 9 refs. concerning allergens and products recently discussed by the authors (5-chloro-1-methyl-4-**nitroimidazole**, 3-dimethylaminopropylamine, fungal .alpha.-amylase, chloramine-T soln., and tri-cure glass ionomer) which cause allergic contact urticaria and allergic contact **dermatitis** upon exposure is given.
ST review allergen exposure health hazard; occupational health hazard allergen exposure review
IT **Dermatitis**
Urticaria
(contact; occupational contact **dermatitis** from exposure to new allergens)
IT Industrial hygiene
Occupational health hazard
(occupational contact **dermatitis** from exposure to new allergens)
IT Allergens
RL: ADV (Adverse effect, including toxicity); TEM (Technical or engineered material use); BIOL (Biological study); USES (Uses)
(occupational contact **dermatitis** from exposure to new allergens)
IT Ionomers
RL: ADV (Adverse effect, including toxicity); TEM (Technical or engineered material use); BIOL (Biological study); USES (Uses)
(tri-cure acrylic glass; occupational contact **dermatitis** from exposure to new allergens)
IT 9000-90-2, .alpha.-Amylase
RL: ADV (Adverse effect, including toxicity); TEM (Technical or engineered material use); BIOL (Biological study); USES (Uses)
(fungal; occupational contact **dermatitis** from exposure to new allergens)
IT 109-55-7, 3-Dimethylaminopropylamine 4897-25-0, 5-Chloro-1-methyl-4-**nitroimidazole**
RL: ADV (Adverse effect, including toxicity); TEM (Technical or engineered material use); BIOL (Biological study); USES (Uses)
(occupational contact **dermatitis** from exposure to new allergens)
IT 127-65-1, Chloramine-T
RL: ADV (Adverse effect, including toxicity); TEM (Technical or engineered material use); BIOL (Biological study); USES (Uses)
(soln.; occupational contact **dermatitis** from exposure to new allergens)
RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Beck, H; Contact Dermatitis 1983, V9, P155 MEDLINE
(2) Dooms-Goossens, A; Contact Dermatitis 1983, V9, P319 MEDLINE
(3) Foti, C; Contact Dermatitis 1995, V33, P132 MEDLINE

(4) Jolanki, R; Contact Dermatitis 1997, V36, P53 CAPLUS
(5) Kanerva, L; Contact Dermatitis 1996, V35, P122 MEDLINE
(6) Kanerva, L; Contact Dermatitis 1997, V37, P180 MEDLINE
(7) Kanerva, L; Contact Dermatitis 1997, V36, P306 MEDLINE
(8) Kanerva, L; Contact Dermatitis 1997, V37, P49 MEDLINE
(9) Lombardi, P; Contact Dermatitis 1989, V20, P302 MEDLINE

L91 ANSWER 13 OF 22 USPATFULL

SUMM The antibacterials useful in the compositions and methods of the present invention include, without limitation, the chlorophors (chlorine releasing agents), phenols, substituted phenols, bisphenols, salicylanilides, hydroxy benzoic acids, polyhydric phenols, hydroxy quinolines, nitroheterocycles, e.g., nitrofurans and **nitroimidazoles**, nalidixic acid, oxolinic acid, quinoxaline- and phenazine-di-N-oxides, iodinin, cotrimoxazole, methenamine, B-lactam antibiotics such as the penicillins, cephalosporins, cephamycins, thienamycins, and clavulanic acid, nocardicins such as cephalothin and cefoxitin, non-lactam antibiotics such as the actinomycin group, bacitracin, tyrothricin, polymyxin and colistin, antibiotic polypeptides with a lactone ring such as etamycin and viridogrisein, staphylomycin, ostreogrycin, doricin, vernamycin, cycloheptamycin, telomycin, rufomycin A, ilamycin, streptogramime, mikamycin, gramicidin, albomycin, bacteriocin, the colicins, edeine, phytoactin, valinomycin, viomycin, the antimycins, distamycin A, neotropsin, thiostrepton, polyene antifungal antibiotics such as nystatin, pimaricin, lucensomycin, rimocidin, amphotericin B, primycin, levorins A and B, candidin, lagosin, filipin, chainim, mycoticin, and flavofungin, macrolide antibiotics such as methymycin, picromycin, lancamycin, oleandomycin, erythromycin, carbomycin, the spiramycins, chalcomycin, borrelidin, tylosin, angolamycin, nonactin, the oligomycins, and maridomycin, aminoglycoside antibiotics such as streptomycin, kanamycin, paromomycin, neomycin, and gentamicin, the tetracyclines, the steroidal antibiotics, the ansamycins such as rifamycin, the streptovaricins, and geldamycin, the glutarimids such as cycloheximide or actidione, naramycin B, antitumor E-73, the streptovitacins, nucleoside antibiotics such as puromycin, tubercidin, angustmycin and psicofurarine, cordycepin, blasticidin, gougerotin, the polyoxins, 3'-amino-3'-deoxyguanosine, nucleocidin, amicetin, sparsomycin; anthracycline antibiotics such as daunomycin, adriamycin, olivomycin, chromomycin and mithramycin, nogalamycin, leukaeomycin, steffimycin, carminomycin I, the phenazines, quinoxaline antibiotics such as echinomycin, the triostins, ionophores such as polyetherin A, monensin, and the nonclassifiable antibiotics such as actinomycetin, actithiazic acid, althiomycin, anthramycin, azaserine, the bleomycins, boromycin, bruneomycin, carzinophilin, cellocidin, chloramphenicol, cycloserine, flavensomycin, fumagillin, griseofulvin, hadacidin, kanchanomycin, lincomycin, micrococcin, the mitomycins, porfiromycin, nalidixic acid, novobiocin, pactamycin, patulin, pluramycin, protoanemonin, pyrrolnitrin, sarkomycin, sibiromycin, the sideromycins, tenuazonic acid, trichothecin, usnic acid, vancomycin and variotin.

SUMM While the choice of any particular agent in the treatment of a specific condition may be dictated by such factors as cost, availability, safety, and the like, such a choice frequently represents the personal experience of the artisan which may or may not be reproduceable. Further, the availability of many actives with equivalent efficacy makes the choice of the "best" specific agent or active, or combination or agents or actives, difficult. However, the selection of an agent, or combination of agents, which can be effectively penetrated to manage any foreseeable condition is well within the skill of the art, and the actual selection of such agents (other than the selection of a penetrable agent or active) plays no part of this invention. For example, when a steroid is incorporated into the compositions of the present invention and the resulting composition is applied to an afflicted/application situs, this invention provides a method for treating and preventing nonendocrine immunologic or rheumatic diseases, such as rheumatoid arthritis, rheumatic fever, disseminated lupus erythematosus, hypersensitivity reactions, such as bronchial asthma, serum sickness, anaphylaxis, bee stings, angioneurotic edema, hay fever, hemolytic enemia, drug reactions and agranulcytosis. Incorporation of a

steroid into the compositions of the present invention and application of the resulting composition to an application situs also provides a method for treating diseases of the liver such as chronic active hepatitis, as well as certain neurological conditions, such as cerebral edema or an increase in intracranial pressure. The incorporation of a steroid and application of the resulting composition to an application situs further provides a method for treating and preventing inflammatory conditions such as ulcerative colitis, **dermatitis** (**atopic**, eczematoid, exfoliative, stasis, nummular, contact, or seborrheic), pemfhigus, gout and other inflammations of skin or mucous membranes caused by chemical, thermal, mechanical or radiant agents. In addition, the present invention may be formulated and used with a steroid in a veterinary context, for example in the treatment of dermatological disorders characterized by inflammation and dry or exudative **dermatitis**, eczematous **dermatitis**, contact **dermatitis**, seborrheic **dermatitis**, and as an adjunct in the treatment of **dermatitis** due to parasitic infestation.

DETD Composition I is applied to a human afflicted with **dermatitis** at the afflicted situs at a rate of 5 mg of composition per square centimeter of skin three times daily for a period of 5 days. Complete elimination of inflammation is noted after 48 hours. Substantially similar results are obtained when the composition is replaced by Compositions II, III, IV or V of Example 1.

ACCESSION NUMBER: 85:72289 USPATFULL
TITLE: Penetrating topical pharmaceutical compositions containing 1-dodecyl-azacycloheptan-2-one
INVENTOR(S): Cooper, Eugene R., Cincinnati, OH, United States
PATENT ASSIGNEE(S): The Procter & Gamble Company, Cincinnati, OH, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4557934		19851210
APPLICATION INFO.:	US 1983-506275		19830621 (6)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Roberts, Elbert L.
LEGAL REPRESENTATIVE: Allen, George W., Goldstein, Steven J., Schaeffer, Jack D.
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 12,14
LINE COUNT: 2057
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The pharmaceutical compositions may be used to treat VLA-4 mediated disease conditions. Such disease conditions include, by way of example, asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes (including acute juvenile onset diabetes), inflammatory bowel disease (including ulcerative colitis and Crohn's disease), multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, stroke, and other cerebral traumas, nephritis, retinitis, **atopic dermatitis**, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome.

SUMM Other heteroaryls may also be employed in the above described reactions including, but not limited to, 2-chloro-4-methyl-3-nitropyridine, 2-chloro-3-nitropyridine (Aldrich Chemical Co.); 4-chloro-3-nitropyridine (J. Med. Chem. 1989, 32, 2474-2485); 4-chloro-5-**nitroimidazole** (J. Chem. Soc. 1930, 268); and the like, to provide compounds of this invention.

SUMM In addition, certain of the compounds of this invention inhibit, in vivo, adhesion of leukocytes to endothelial cells mediated by VLA-4 and, accordingly, can be used in the treatment of diseases mediated by VLA-4. Such diseases include inflammatory diseases in mammalian patients such as asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes (including acute juvenile onset diabetes), inflammatory bowel disease (including ulcerative colitis and Crohn's disease), multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, stroke, and other cerebral traumas, nephritis, retinitis, **atopic dermatitis**, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome.

SUMM The pharmaceutical compositions of the present invention can be used to block or inhibit cellular adhesion associated with a number of diseases and disorders. For instance, a number of inflammatory disorders are associated with integrins or leukocytes. Treatable disorders include, e.g., transplantation rejection (e.g., allograft rejection), Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes (including acute juvenile onset diabetes), retinitis, cancer metastases, rheumatoid arthritis, acute leukocyte-mediated lung injury (e.g., adult respiratory distress syndrome), asthma, nephritis, and acute and chronic inflammation, including **atopic dermatitis**, psoriasis, myocardial ischemia, and inflammatory bowel disease (including Crohn's disease and ulcerative colitis). In preferred embodiments the pharmaceutical compositions are used to treat inflammatory brain disorders, such as multiple sclerosis (MS), viral meningitis and encephalitis. Inflammatory bowel disease is a collective term for two similar diseases referred to as Crohn's disease and ulcerative colitis. Crohn's disease is an idiopathic, chronic ulceroconstrictive inflammatory disease characterized by sharply delimited and typically transmural involvement of all layers of the bowel wall by a granulomatous inflammatory reaction. Any segment of the gastrointestinal tract, from the mouth to the anus, may be involved, although the disease most commonly affects the terminal ileum and/or colon. Ulcerative colitis is an inflammatory response limited largely to the colonic mucosa and submucosa. Lymphocytes and macrophages are numerous in lesions of inflammatory bowel disease and may contribute to inflammatory injury.

ACCESSION NUMBER: 2002:297585 USPATFULL
TITLE: Compounds which inhibit leukocyte adhesion mediated by VLA-4
INVENTOR(S): Konradi, Andrei W., San Francisco, CA, United States
Pleiss, Michael A., Sunnyvale, CA, United States
Thorsett, Eugene D., Half Moon Bay, CA, United States

Ashwell, Susan, Plainsboro, NJ, United States
Sarantakis, Dimitrios, Newtown, PA, United States
Welmaker, Gregory S., Jackson, NJ, United States
Kreft, Anthony, Langhorne, PA, United States
Semko, Christopher, Fremont, CA, United States
Sullivan, Robert Warren, Oceanside, CA, United States
Soares, Christopher Joseph, La Jolla, CA, United States
Ly, Kiev Sui, San Diego, CA, United States
Tarby, Christine M., Hockessin, DE, United States
PATENT ASSIGNEE(S): Elan Pharmaceuticals, Inc., So. San Francisco, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6479492	B1	20021112	
APPLICATION INFO.:	US 2000-489378		20000121	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1999-116923P	19990122	(60)
	US 1999-160999P	19991021	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Shah, Mukund J.

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      (FILE 'HOME' ENTERED AT 12:11:40 ON 10 JUL 2003)

      FILE 'USPATFULL, CAPLUS' ENTERED AT 12:11:58 ON 10 JUL 2003

      FILE 'REGISTRY' ENTERED AT 12:12:04 ON 10 JUL 2003
L1             1 S TINIDAZOLE/CN

      FILE 'CAPLUS' ENTERED AT 12:12:40 ON 10 JUL 2003
L2           662 S L1
L3           211 S L1/USES
L4            13 S L3 AND (SKIN)

      FILE 'USPATFULL' ENTERED AT 12:18:21 ON 10 JUL 2003
L5           200 S TINIDAZOLE OR L1 OR FASIGIN OR GLONGYN OR PLETIL OR SORQUETAN
L6            74 S L5 AND TREAT? AND  SKIN
L7            34 S L6 AND DERMAT?

=> save all
ENTER NAME OR (END):l10046575/l
L# LIST L1-L7 HAS BEEN SAVED AS 'L10046575/L'

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L55 ANSWER 4 OF 8 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 81094292 EMBASE
DN 1981094292
TI Effects of simple imidazoles on human peripheral blood lymphocytes stimulated by mitogen or allogeneic cells.
AU Miller J.J.; Reeves S.C.; Salaman J.R.
CS K.R.U.F., Inst. Renal Dis., Cardiff Roy. Infirm., Cardiff, United Kingdom
SO Journal of Immunopharmacology, (1980) 2/2 (225-243).
CODEN: JOIMD6
CY United States
DT Journal
FS 030 Pharmacology
037 Drug Literature Index
026 Immunology, Serology and Transplantation
025 Hematology
LA English
AB Five imidazole compounds were added to cultures of human lymphocytes which had been stimulated to undergo blast transformation by exposure to phytohaemagglutinin, pokeweed mitogen or allogeneic cells. Two compounds, clotrimazole and dacarbazine (DTIC) produced a dose related suppression of these responses. Nimorazole was largely inactive whereas metronidazole and **tinidazole** actually enhanced the response - at least in those cultures stimulated by the plant mitogens. It is suggested that experiments of this kind are helpful in identifying those imidzaole compounds that could be used as **immunosuppressants** in vivo.
CT Medical Descriptors:
*allogenic cell
*lymphocyte transformation
*immunosuppressive treatment
*lymphocyte
*lymphocyte culture
thymidine h 3
in vitro study
human cell
blood and hemopoietic system
normal human
lymphatic system
Drug Descriptors:
*clotrimazole
*dacarbazine
*imidazole derivative
*metronidazole
*nimorazole
*tinidazole
niridazole
phytohemagglutinin
pokeweed mitogen
radioisotope
nagoxin
unclassified drug
RN (clotrimazole) 23593-75-1; (dacarbazine) 4342-03-4; (metronidazole) 39322-38-8, 443-48-1; (nimorazole) 6506-37-2; (tinidazole) 19387-91-8; (niridazole) 61-57-4; (phytohemagglutinin) 9008-97-3; (pokeweed mitogen) 63231-57-2
CN Ambilhar; Simplotan; Nagoxin; Canesten
CO May and baker (United Kingdom); Bayer (United Kingdom); Wellcome (United Kingdom); Pfizer (United Kingdom); Amersham (United Kingdom); Gibco (United Kingdom); Montedison (United Kingdom)

L63 ANSWER 8 OF 11 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 83024992 EMBASE
DN 1983024992
TI [Vulvovaginitis in childhood, experiences of a gynecologic pediatric clinic].
DIE VULVOVAGINITIS IM KINDESALTER. ERFAHRUNGEN EINER KINDERGYNAKOLOGISCHEN AMBULANZ.
AU Boschitsch E.; Gerstner G.; Grunberger W.
CS I Frauenklin., Univ. Wien, Austria
SO Fortschritte der Medizin, (1982) 100/37 (1703-1708).
CODEN: FMDZAR
CY Germany
DT Journal
FS 037 Drug Literature Index
010 Obstetrics and Gynecology
007 Pediatrics and Pediatric Surgery
LA German
SL English
CT Medical Descriptors:
*childhood
***dermatitis**
*diaper
*newborn
*drug therapy
*prepuberty
*vulvovaginitis
diagnosis
etiology
therapy
short survey
human
child
female genital system
Drug Descriptors:
*dequalinium
*idoxuridine
*ketoconazole
*metronidazole
*miconazole
*neomycin
*penicillin g
*podophyllin
*povidone iodine
*pyrantel
*spectinomycin
*tetracycline
***tinidazole**
nystatin
dequavagin
pyrantel embonate
unclassified drug
RN (dequalinium) 4028-98-2, 522-51-0, 6707-58-0, 8054-75-9; (idoxuridine) 54-42-2; (ketoconazole) 65277-42-1; (metronidazole) 39322-38-8, 443-48-1; (miconazole) 22916-47-8; (neomycin) 11004-65-2, 1404-04-2, 1405-10-3, 8026-22-0; (penicillin g) 1406-05-9, 61-33-6; (podophyllin) 9000-55-9; (povidone iodine) 25655-41-8; (pyrantel) 15686-83-6, 26155-20-4; (spectinomycin) 1695-77-8, 21736-83-4, 23312-56-3; (tetracycline) 23843-90-5, 60-54-8, 64-75-5; (**tinidazole**) 19387-91-8; (nystatin) 1400-61-9, 34786-70-4, 62997-67-5; (pyrantel embonate) 22204-24-6
CN Betaisodona; Mycostatin; Dequavagin; Moronal; Combantrin; Nizoral; Helmex; Stanilo; Fasigyn; Trobicin; Simplotan; Clont
CO Pfizer (Germany); Von heyden (Germany); Breussle

L63 ANSWER 7 OF 11 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 83205818 EMBASE
DN 1983205818
TI [Contact sensitivity to antimycotic imidazole derivates].
KONTAKTALLERGIEN GEGENUBER IMIDAZOLHALTIGEN ANTIMYKOTIKA.
AU Jelen G.
CS 20 Rue des Clefs, F-67700 Saverne, France
SO Hautarzt, (1983) 34/8 (423).
CODEN: HAUTAW
CY Germany
DT Journal
FS 038 Adverse Reactions Titles
037 Drug Literature Index
LA German
CT Medical Descriptors:
*adverse drug reaction
***contact dermatitis**
*drug hypersensitivity
*skin toxicity
intoxication
topical drug administration
editorial
human
fungus
Drug Descriptors:
*antifungal agent
*clotrimazole
*econazole
*isoconazole
*mebendazole
*metronidazole
*miconazole
*nimorazole
***tinidazole**
RN (clotrimazole) 23593-75-1; (econazole) 24169-02-6, 27220-47-9; (isoconazole) 24168-96-5, 27523-40-6; (mebendazole) 31431-39-7; (metronidazole) 39322-38-8, 443-48-1; (miconazole) 22916-47-8; (nimorazole) 6506-37-2; (**tinidazole**) 19387-91-8

L63 ANSWER 6 OF 11 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 1998245603 EMBASE
TI Cutaneous lesions in giardiasis. Report of two cases [1].
AU Sanchez-Carpintero I.; Vazquez-Doval F.J.
CS I. Sanchez-Carpintero, Department of Dermatology, University Clinic of Navarra, University of Navarra, PO Box 192, E-31080 Pamplona, Navarra, Spain
SO British Journal of Dermatology, (1998) 139/1 (152-153).
Refs: 10
ISSN: 0007-0963 CODEN: BJDEAZ
CY United Kingdom
DT Journal; Letter
FS 013 Dermatology and Venereology
037 Drug Literature Index
LA English
CT Medical Descriptors:
*giardiasis: DI, diagnosis
*giardiasis: DT, drug therapy
skin manifestation
urticaria
mouth ulcer
atopic dermatitis
follow up
endoscopy
allergenicity
human
male
female
case report
adult
letter
priority journal
Drug Descriptors:
*metronidazole: DO, drug dose
*metronidazole: DT, drug therapy
***tinidazole: DO, drug dose**
***tinidazole: DT, drug therapy**
immunoglobulin e
RN (metronidazole) 39322-38-8, 443-48-1; (**tinidazole**) 19387-91-8; (immunoglobulin e) 37341-29-0

L79 ANSWER 11 OF 61 USPATFULL

DETD The use of ketoconazole or **metronidazole** for the **treatment** of seborrheic **dermatitis** or psoriasis requires merely taking one or two tablets a day before meals for a period of some two to twenty weeks. No special precautions are required other than the ordinary ones which presently accompany the drugs when used for control of yeast, fungal and bacterial infections. No special laboratory testing of patients is required. Evaluation of the effectiveness of the medication is by simple inspection of the patient and by changes in the amounts of itching present.

CLM What is claimed is:

1. A method of **treating** psoriasis or seborrheic **dermatitis** in humans comprising the oral administration of an effective, lesion reducing, amount of an imidazole antibiotic to said humans, said imidazole antibiotic being selected from the group consisting of ketoconazole and **metronidazole**.

PI US 4491588 19850101

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L79 ANSWER 10 OF 61 USPATFULL

AB Topical aqueous single-phase compositions containing **metronidazole** are disclosed. The compositions have improved specific activity and are substantially non-comedogenic, non-irritating and non-skin-drying. These aqueous topical compositions are particularly useful for **treating** rosacea and other acneform dermatological conditions, and certain forms of **dermatitis**.

SUMM **Metronidazole**, 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole, is a drug known to be effective in **treating** a variety of disorders. For example, the drug has direct trichomonacidal and amebacidal activity against Trichomonas vaginalis and Entamoeba histolytica, and is useful in combatting infections caused by those microbial parasites. **Metronidazole** has also been reported to be effective (via both oral and topical application) in **treating** skin disorders such as rosacea, ulcers infected with anaerobic bacteria, including decubitus ulcers (bed or pressure sores), venous ulcers, and diabetic foot ulcers, and other anaerobic infections such as post operative sepsis. There have also been reports that **metronidazole** is effective against perioral **dermatitis**

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SUMM Rosacea, formerly called Acne rosacea, is a chronic skin disease primarily affecting adults, with recurring symptoms that include erythema, papules, pustules, rhinophyma, and telangiectses, primarily in the region of the nose, cheeks, and forehead. In rosacea, other acneform conditions, and certain types of **dermatitis**, topical **treatment** compositions are usually applied to both unafflicted and diseased areas. It is therefore desirable that a **treatment** have a mitigating effect on the diseased tissue and a prophylactic effect to prevent extension of involvement to the unafflicted tissue. Therefore, the preferred vehicles, and hence compositions, to obtain these desirable effects should contain **metronidazole** in a high thermodynamic activity and with a fast rate of release from the vehicle. Aqueous compositions of **metronidazole** would appear to meet the above criteria. However, the low solubility of **metronidazole** in water and several other solvents inhibits the preparation of an aqueous compositions. This has resulted in the development of oil-based, rather than aqueous, **metronidazole** compositions.

SUMM Thus, a need remains for **metronidazole**-containing dermatological preparations suitable for topical use which avoid the problems of current compositions. Such dermatological preparations would be useful for **treating** skin disorders such as rosacea and certain types of **dermatitis**, including perioral **dermatitis**. The present invention provides such preparations.

CLM What is claimed is:

15. A method for **treatment** of a human afflicted with a skin disorder which is a member of the group consisting of acne, rosacea, perioral **dermatitis** and seborrheic **dermatitis**, said method comprising topically applying to the afflicted skin region a therapeutically effective amount of a dermatological preparation in the form of an aqueous gel composition comprising: a therapeutically effective amount of **metronidazole** as the sole active ingredient; a gelled hydrophilic and water-dispersible polymer having free carboxylic groups which is a polyacrylic acid polymer having a molecular weight in the range of about 1,250,000 to about 4,000,000 daltons; and an aqueous solvent for said metronidazole.

PI US 4837378 19890606

L79 ANSWER 5 OF 61 USPATFULL

SUMM **Metronidazole**, 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole, has long been known as an effective drug to **treat** a variety of disorders, and is especially well known for the **treatment** of various protozoal diseases. As a topical therapy, **metronidazole** has also been shown to be useful in **treating** various skin disorders, including acne rosacea, bacterial ulcers, and perioral **dermatitis**. See, Borgman, U.S. Pat. No. 4,837,378. **Metronidazole** has been found to have an anti-inflammatory activity when used topically to **treat** dermatologic disorders. See, Czernielewski, et al., U.S. Pat. No. 5,849,776. **Metronidazole** may also be used as an intravaginal therapeutic agent for the **treatment** of bacterial vaginosis. See, Borgman, U.S. Pat. No. 5,536,743.

PI US 6468989 B1 20021022

ANSWER 2 OF 61 USPATFULL

SUMM [0028] However, in those references mentioned above pertaining to immunity, with the exception of the Int. J. Radiation Oncology Biol. Phys., 9, 701 (1983), all of the immune reactions observed are immune reactions other than on the skin surface. In addition, the observed immunosuppressive effects are remarkably lower in comparison with those of immunosuppressants used clinically, and it is therefore considered that external preparations of **metronidazole** or tinidazole cannot be expected to be effective as therapeutic agents for atopic **dermatitis**. Further, there is no correlation between the effectiveness in **treatment** of atopic **dermatitis** and the effectiveness in the model of contact **dermatitis** used in the Int. J. Radiation Oncology Biol. Phys., 701 (1983) in which the only immune reaction on the skin surface is observed. Moreover, it has not been known that typical therapeutic agents for inflammatory disease are used for therapeutic **treatment** of atopic **dermatitis**. In addition, the use of a nitroimidazole derivative for **treatment** of atopic **dermatitis** is also previously unknown.

SUMM [0029] Further, U.S. Pat. No. 4,491,588 discloses the **treatment** of psoriasis by oral administration of **metronidazole**, and although ketoconazole, which is similarly disclosed as being effective in the **treatment** of psoriasis, has been granted a right as an oral preparation (U.S. Pat. No. 4,491,588) and as an external preparation (U.S. Pat. No. 4,569,935), only an oral preparation has been granted a right with respect to **metronidazole**. The present invention is directed to findings that an external preparation of **metronidazole** is superior to the oral preparation in terms of effect and toxicity. Moreover, since the therapeutic use for psoriasis indicated in International Unexamined Patent Publication No. WO96/01117 is one example of a typical inflammatory disease, and the disclosed contents merely indicate that an external preparation of **metronidazole** is able to inhibit the formation of edema caused by local stimulation by arachidonic acid, as was described by the applicant himself to the effect that, "conventional non-steroid anti-inflammatory drugs, such as cyclooxygenase or lipoxygenase reaction inhibitors (including indometacin, naproxen and phenylbutazone) and preparations able to inhibit conduit plasma backflow (such as vasoconstrictors) are excellent reaction inhibitors in this model", this is an experimental system in which conventional non-steroid anti-inflammatory drugs (NSAIDs) also exhibit excellent effect. In this publication, it is deduced that **metronidazole** can be used for the **treatment** of "eczema, psoriasis, rosacea, lupus vulgaris, ulcers and seborrheic **dermatitis**", etc. only by virtue of confirming its action. However, this patent application cannot be included in a prior art reference of the present application since the etiology of psoriasis is unknown, nearly all NSAIDs do not exhibit therapeutic effects against psoriasis and the therapeutic effect against psoriasis has actually not been confirmed.

SUMM [0111] an external preparation for a therapeutic or prophylactic **treatment** of (10) atopic **dermatitis** in which the nitroimidazole derivative is **metronidazole**,

SUMM [0112] an external preparation for a therapeutic or prophylactic **treatment** of (11) facial atopic **dermatitis** in which the nitroimidazole derivative is **metronidazole**,

SUMM [0113] an external preparation for a therapeutic or prophylactic **treatment** of (12) pediatric atopic **dermatitis** in which the nitroimidazole derivative is **metronidazole**,

SUMM [0117] an external preparation for a therapeutic or prophylactic

treatment of (10) atopic **dermatitis** in which the nitroimidazole derivative is **metronidazole**, and **metronidazole** and an antimycotic agent, immunosuppressant, steroid or their combination being administered simultaneously or separately with an interval,

SUMM [0118] an external preparation for a therapeutic or prophylactic **treatment** of (10) atopic **dermatitis** in which the nitroimidazole derivative is **metronidazole**, and **metronidazole** and immunosuppressant, steroid, or a combination of antimycotic agent and steroid being administered simultaneously or separately with an interval,

PI US 2003092754 A1 20030515

L20 ANSWER 7 OF 21 USPATFULL

DETD A number of the compounds encompassed in the present invention have been found to have **immunosuppressant** action. Of those tested, most of these are of the 4-substituted imidazo[1,2-a]quinoxaline type described in formula I above, although a couple are of the 1-(2-acylaminophenyl)**imidazole** type shown in formula II. Because they exhibit this activity, they are indicated for use in the **treatment** of those diseases that the prior art recognizes may be helped by the administration of **immunosuppressants**. These include such conditions as: glomerulonephritis, serum sickness, organ transplant, rheumatoid arthritis, systemic lupus erythematosis, ulcerative colitis, chronic active hepatitis, multiple sclerosis, heterografts or homografts in burns, psoriatic arthritis, urticaria, respiratory allergies, i.e. asthma, hayfever; scleraclerma, mycosis fungoides, dermatomyositis, psoriasis and contact **dermatitis** (including poison ivy).

ACCESSION NUMBER: 80:59271 USPATFULL

TITLE: 1-(2-Acylaminophenyl)imidazoles

INVENTOR(S): Warner, Jr., Paul L., Clarence, NY, United States
Luber, Jr., Edward J., Buffalo, NY, United States

PATENT ASSIGNEE(S): Westwood Pharmaceuticals, Inc., Buffalo, NY, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4236015		19801125
APPLICATION INFO.:	US 1979-36471		19790507 (6)

RELATED APPLN. INFO.: Division of Ser. No. US 1977-858514, filed on 8 Dec 1977, now patented, Pat. No. US 4172947, issued on 30 Oct 1979 which is a continuation-in-part of Ser. No. US 1977-757640, filed on 7 Jan 1977, now abandoned

DOCUMENT TYPE: Utility

L20 ANSWER 6 OF 21 USPATFULL

SUMM a) Autoimmune diseases and inflammatory conditions, e.g., various pains collagen diseases, autoimmune diseases, various immunity diseases, and the like in human beings or animals, and more particularly for the treating and/or preventing inflammation and pain in joint and muscle (e.g. rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, etc.), inflammatory skin condition (e.g. sunburn, eczema, etc.), inflammatory eye condition (e.g. conjunctivitis, etc.), lung disorder in which inflammation is involved (e.g. asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.), condition of the gastrointestinal tract associated with inflammation (e.g. aphthous ulcer, Crohn's disease, atrophic gastritis, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.), gingivitis, (inflammation, pain and tumescence after operation or injury), pyrexia, pain and other conditions associated with inflammation, systemic lupus erythematosus, scleroderma, polymyositis, polychondritis, periarteritis nodosa, ankylosing spondylitis, inflammatory chronic renal condition (e.g. nephrotic syndrome, glomerulonephritis, membranous nephritis, etc.), acute nephritis, rheumatic fever, Sjogren's syndrome, Behcet disease, thyroiditis, type I diabetes, dermatomyositis, chronic active hepatitis, acute hepatitis, myasthenia gravis, idiopathic sprue, Grave's disease, multiple sclerosis, primary billiary cirrhoris, Reiter's syndrome, autoimmune hematological disorders (e.g. hemolytic anemia, pure red cell anemia, idiopathic thrombocytopenia; aplastic anemia, etc.), myasthenia gravis, uveitis, contact **dermatitis**, psoriasis, Kawasaki disease, sarcoidosis, Wegner's granulomatosis, Hodgkin's disease, or the like;

DETD The **imidazole** compounds of the present invention have ADA inhibitory activity and can thus elevate Ado concentration. Since Ado is effective for immunomodulation, especially **immunosuppression**, antiinflammation and **treatment** and prevention of various diseases, the **imidazole** compounds of the present invention are useful for **treating** or preventing diseases for which Ado is effective.

ACCESSION NUMBER: 2002:57963 USPATFULL
TITLE: Imidazole compounds
INVENTOR(S): Terasaka, Tadashi, Ikeda, JAPAN
Nakamura, Katsuya, Takatsuki, JAPAN
Seki, Nobuo, Takarazuka, JAPAN
Kuno, Masako, Amagasaki, JAPAN
Tsujimoto, Susumu, Fujiidera, JAPAN
Sato, Akihiro, Kobe, JAPAN
Nakanishi, Isao, Tenri, JAPAN
Kinoshita, Takayoshi, Tsukuba, JAPAN
Nishio, Nobuya, Yawara-mura, JAPAN
Okumura, Hiroyuki, Osaka, JAPAN
Tsuji, Kiyoshi, Kishiwada, JAPAN
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Osaka, JAPAN (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6359145	B1	20020319	
	WO 2000005217		20000203	
APPLICATION INFO.:	US 2001-764995		20010309	(9)
	WO 1999-JP3939		19990722	
			20010309	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	AU 1998-4840	19980723
	AU 1998-7355	19981127

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Higel, Floyd D.
ASSISTANT EXAMINER:	Shameem, Golam M. M.
LEGAL REPRESENTATIVE:	Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
NUMBER OF CLAIMS:	11

L20 ANSWER 5 OF 21 USPATFULL

SUMM [0017] Furthermore, the very recent cloning of IK.sub.Ca has enabled the demonstration of the mRNA for this gene in several organs including placenta, salivary glands, lung and pancreas. Thus, specific blockers of IK.sub.Ca are likely to be very effective as **immunosuppressive** agents, and devoid of side effects on excitable tissue. In fact, the IK.sub.Ca-inhibitor **Clotrimazole** (which is also a blocker of the cytochrome P-450 system) has been extensively used clinically in the systemic **treatment** of fungal infections. No toxicity related to K-channel blockade has been described.

SUMM [0198] Conditions which may benefit from this treatment include, but are not limited to diseases, disorders or conditions such as autoimmune diseases, e.g. Addison's disease, alopecia areata, Ankylosing spondylitis, hemolytic anemia (anemia haemolytica), pernicious anemia (anemia perniciosa), aphthae, aphthous stomatitis, arthritis, osteoarthritis, rheumatoid arthritis, aspermiogenese, asthma bronchiale, autoimmune asthma, autoimmune hemolysis, Bechet's disease, Boeck's disease, inflammatory bowel disease, Burkitt's lymphoma, Chron's disease, chorioiditis, colitis ulcerosa, Coeliac disease, cryoglobulinemia, **dermatitis** herpetiformis, dermatomyositis, insulin-dependent type I diabetes, juvenile diabetes, idiopathic diabetes insipidus, insulin-dependent diabetes mellisis, autoimmune demyelinating diseases, Dupuytren's contracture, encephalomyelitis, encephalomyelitis allergica, endophthalmia phacoanaphylactica, enteritis allergica, autoimmune enteropathy syndrome, erythema nodosum leprosum, idiopathic facial paralysis, chronic fatigue syndrome, febris rheumatica, glomerulo nephritis, Goodpasture's syndrome, Graves'disease, Hamman-Rich's disease, Hashimoto's disease, Hashimoto's thyroiditis, sudden hearing loss, sensoneural hearing loss, hepatitis chronica, Hodgkin's disease, haemoglobinuria paroxysmatica, hypogonadism, ileitis regionalis, iritis, leucopenia, leucemia, lupus erythematosus disseminatus, systemic lupus erythematosus, cutaneous lupus erythematosus, lymphogranuloma malignum, mononucleosis infectiosa, myasthenia gravis, traverse myelitis, primary idiopathic myxedema, nephrosis, ophthalmia symphatica, orchitis granulomatosa, pancreatitis, pemphigus, pemphigus vulgaris, polyarteritis nodosa, polyarthritis chronica primaria, polymyositis, polyradiculitis acuta, psoreasis, purpura, pyoderma gangrenosum, Quervain's thyreoiditis, Reiter's syndrome, sarcoidosis, ataxic sclerosis, progressive systemic sclerosis, scleritis, sclerodermia, multiple sclerosis, sclerosis disseminata, acquired spenic atrophy, infertility due to antispermatozoan antobodies, thrombocytopenia, idiopathic thrombocytopenia purpura, thymoma, acute anterior uveitis, vitiligo, AIDS, HIV, SCID and Epstein Barr virus associated diseases such as Sjorgren's syndrome, virus (AIDS or EBV) associated B cell lymphoma, parasitic diseases such as Lesihmania, and immunosuppressed disease states such as viral infections following allograft transplantations, graft vs. Host syndrome, transplant rejection, or AIDS, cancers, chronic active hepatitis diabetes, toxic chock syndrome, food poisoning, and transplant rejection.

ACCESSION NUMBER: 2002:221846 USPATFULL
TITLE: Chemical compounds having ion channel blocking activity for the treatment of immune dysfunction
INVENTOR(S): Jensen, Bo S., Kobenhavn S, DENMARK
Olsen, Soren-Peter, Klampenborg, DENMARK
Jorgensen, Tino D., Solrod Strand, DENMARK
Strobaek, Dorte, Farum, DENMARK
Christophersen, Palle, Ballerup, DENMARK

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002119989	A1	20020829

	US 6545028	B2	20030408
APPLICATION INFO.:	US 2000-550645	A1	20000414 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. WO 1998-DK490, filed on 13 Nov 1998, UNKNOWN		

	NUMBER	DATE
PRIORITY INFORMATION:	DK 1997-1298	19971114

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BIRCH STEWART KOLASCH & BIRCH, PO BOX 747, FALLS CHURCH, VA, 22040-0747
NUMBER OF CLAIMS: 32
EXEMPLARY CLAIM: 1
LINE COUNT: 1464
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The FDA approved prescription therapeutic compounds that can be included in the formulations of the invention for **treating** epithelial diseases such as those described herein include, for example: nonsteroidal antiinflammatory agents, **immunosuppressives**, corticosteroids, antimicrobials, chemotherapeutics, vitamin D analogs and retinoids. The preferred compounds include dapsone, meselamine, sulfasalazine, sulfacetamide, silver sulfadiazine, colchicine, calcipotriene, calcipitriol, ibuprofen, flubiprofen, ketoprofen, indomethacin, piroxicam, ketorolac, chloroquine, quinacrine, hydroxy-chloroquine, triamcinolone, flurandrenolide, prednicarbate, halcinonide, alclometasone, hydocortisone, desonide, amcinonide, fluocinonide, diflorasone, betamethasone, dexamethasone, desoximetasone, fluticasone, mometisone, fluocinolone, cyclosporin, ascomycin, rapamycin, tacrolimus, erythromycin, clindamycin, lincomycin, vancomycin, ciprofloxacin, ofloxacin, norfloxacin, doxycycline, meclomycin, tetracycline, minocycline, methotrexate, mercaptopurine, hydroxyurea, azathioprine, bleomycin, cyclophosphamide, 5-fluorouracil, cis-platinin, chlorambucil, nitrogen mustard, carmustine, doxorubicin, daonorubicin, anthralin, transretinoic acid, etretinate, acitretin, isotretinoin, adapalene, tazarotene, **metronidazole**, terbenifine, ketoconazole, oxiconazole, sulconozole, fluconazole, itraconazole, griseofulvin, cicloprix, clotrimizole, econazole, miconazole, azelaic acid, benzoyl peroxide, gramicidin, bacitracin, polymixin, nystatin, tobramycin, gentamicin, chloramphenicol, amphotericin, dicloxacillin, carbenicillin, ampicillin, amoxicillin, amoxicillin-clavulanate, cephalexin, cefixime, cefuroxime, cephadroxil, and mupirocin. The FDA over-the-counter monograph allowed therapeutic compounds for dandruff, psoriasis and seborrheic **dermatitis** include hydrocortisone, resorcinol, salicylic acid, and sulfur in addition to zinc pyrithione and selenium sulfide which are included in this invention. The preceding list of the approved prescription and OTC therapeutic compounds for epithelial diseases is for example only and is not intended to be all inclusive for the FDA-approved and FDA-monographed compounds.

SUMM This invention does not include topical formulations that contain zinc pyrithione or selenium sulfide as the only active ingredient to treat psoriasis, dandruff and seborrheic **dermatitis**, or zinc pyrithione and clobetasol to treat psoriasis.

DETD Three patients suffering from frequently recurrent facial seborrheic **dermatitis** and moderate signs of aging applied Formulation C twice daily for sixteen weeks. There was complete clearing of the **dermatitis** within four weeks, and no recurrences during the sixteen week period. All patients experienced improved texture, decreased roughness, and diminished fine wrinkles.

DETD Two patients suffering from facial seborrheic **dermatitis** were treated with Formulation G twice daily. Both experienced complete clearing within two weeks of use.

DETD Three patients suffering from recurrent atopic **dermatitis** were treated with Formulation I twice daily. Complete clearing of the **dermatitis** was achieved within two weeks and no recurrences developed over the following four months.

ACCESSION NUMBER: 2002:304005 USPATFULL

TITLE: Pyridine-thiols for treatment of a follicular dermatosis

INVENTOR(S): Thornfeldt, Carl R., Nampa, ID, United States

PATENT ASSIGNEE(S): Cellegy Pharmaceuticals, Inc., Foster City, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6482839	B1	20021119

APPLICATION INFO.:	US 1998-145822	19980902 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. WO 1998-US11270, filed on 2 Jun 1998 Continuation-in-part of Ser. No. US 1998-89302, filed on 1 Jun 1998	

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-47360P	19970602 (60)
	US 1997-56282P	19970903 (60)
	US 1997-58752P	19970912 (60)
	US 1997-56290P	19970903 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Webman, Edward J.
LEGAL REPRESENTATIVE:	Townsend and Townsend and Crew, LLP
NUMBER OF CLAIMS:	16

L28 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2003 ACS
AN 1991:597967 CAPLUS
DN 115:197967
TI Effects of some imidazoles on cellular immune responses - an experimental study
AU Sen, P.; Chakravarty, A. K.; Kohli, J.
CS Dep. Pharmacol., Univ. Coll. Med. Sci., Delhi, 110 095, India
SO Indian Journal of Experimental Biology (1991), 29(9), 867-9
CODEN: IJEBA6; ISSN: 0019-5189
DT Journal
LA English
CC 1-7 (Pharmacology)
AB Effects of some imidazole compds. were studied on two animal models of cellular immune responses. Metronidazole in doses of 100 and 200 mg/kg and cimetidine 200 mg/kg (i.p.), significantly suppressed the delayed type of hypersensitivity reaction, as evidenced by the footpad thickness method in mice. No significant alteration in the response could be obsd. however, in tinidazole treated groups. All the three drugs inhibited the migration of leukocytes in the presence of antigen in rats considerably. However, they did not produce any involution of spleen or redn. of adrenal wt. indicating that their actions are not corticosteroid mediated. All the three drugs studied are histamine-like imidazole derivs. H2 receptors are present on the surface of T-lymphocytes. They appear to modulate the cellular immune response by altering the function of the regulatory lymphocytes.
ST imidazole deriv cimetidine metronidazole **tinidazole** **immunosuppressant**
IT Immunosuppressants
(imidazole compds. as, hypersensitivity reaction and leukocyte migration inhibited by)
IT Leukocyte
(migration of, imidazole compds. inhibition of, immunosuppression in relation to)
IT Allergy
(hypersensitivity, imidazole compds. inhibition of, immunosuppression in relation to)
IT 288-32-4D, Imidazole, derivs. 443-48-1, Metronidazole 19387-91-8, **Tinidazole** 51481-61-9, Cimetidine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**immunosuppressant** activity of, hypersensitivity reaction and leukocyte migration inhibited by)

=>

The methods of the present invention may also be used to treat atopic states, e.g., atopic allergies such as **dermatitis**. The peptides of the instant invention may be useful for decreasing or deviating an ongoing immune response, e.g. synthesis of IgE that mediates allergy. "Modulating" is intended to mean increasing or decreasing the magnitude of an immune response and "deviation" is used, as in "immune deviation", to mean a redirecting of an ongoing immune response, e.g. redirected from an immune response directed toward a first antigen to a response directed to a second antigen; or, redirected from production of IgE to production of IgG; or e.g., redirected from a humoral response to a cell-mediated immune response. Immune deviation using the subject pharmaceutical preparations may prove useful for treating diseases e.g. acute allergic reactions, chronic urticaria, atopic **dermatitis**, and the like.

DETD Test parameters measured in this study included differential blood cell counts, cellular lysosomal cationic protein levels (i.e., a measure of neutrophil activation and nonspecific resistance to infection), "Activated" **T-lymphocytes** (i.e., **T**-cell rosetting to trypsinized sheep red blood cells), "Total" CD2.sup.+ **T-lymphocytes** (E.sub.s -RFC), C3b-receptor bearing lymphocytes, i.e., B-lymphocytes (E.sub.s AC-RFC). The latter parameters were measured for lymphocyte populations in peripheral blood, thymus, lymph nodes, spleen and red bone marrow. Functional tests of peripheral blood lymphocytes included cytokine measurement, i.e., synthesis of **Leukocyte Migration** Inhibition Factor (LMIF) after in vitro stimulation with Con-A.

DETD Guinea pigs (250-300 gm) were X-irradiated at a total body dose of 1 Gy using a target-to-**skin** distance of 70 cm, a time of exposure of 2 minutes 48 seconds, and an RUM-17 irradiator with parameters set at: 180 kV; 15 mA; 0.5 Cu filter; 1 Al; and, dose output 35.8 P/min. HM897 treatments were administered to animals in the experimental group (n=8) on a daily baisis i.m. as a single 1 .mu.g/kg dose beginning on the day following the irradiation. Animals in the irradiated control group (n=12) were treated using the same regimen but with normal saline 0.5 ml i.m., instead of HM897. Twelve non-irradiated normal animals served as normal treatment vehicle-controls and they were treated with saline only on the same treatment regimen (non-irradiated control). Leukocyte and lymphocyte levels were measured in peripheral blood and in thymus, spleen, lymph nodes, and bone marrow on the 8th and 21st days after the irradiation. The experiment was repeated three times. Illustrative effects of HM897 treatments on the populations of immune cells in various lymphoid organs are shown in TABLE 2, i.e., illustrative results of two (of the three) experiments are presented.

DETD Peripheral blood was obtained from patients with streptococcal and staphylococcal **skin** disease and lymphocytes prepared by Ficoll-Hypaque density sedimentation according to the method of Boyum. The percentage of lymphocytes bearing cell surface immunoglobulin (SIg+), IgM, IgG, and IgA were determined by imunofluorescence microscopy using FITC-conjugated isotype-specific antibodies. Cell surface expression of immunoglobulin markers on B-lymphocytes was determined before and after incubation in vitro with HM897 at a concentration of 1 .mu.g/ml in tissue culture medium. The results are presented in TABLE 5, below.

PI US 6100380 20000808

L79 ANSWER 10 OF 61 USPATFULL

AB Topical aqueous single-phase compositions containing **metronidazole** are disclosed. The compositions have improved specific activity and are substantially non-comedogenic, non-irritating and non-skin-drying. These aqueous topical compositions are particularly useful for **treating** rosacea and other acneform dermatological conditions, and certain forms of **dermatitis**.

SUMM **Metronidazole**, 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole, is a drug known to be effective in **treating** a variety of disorders. For example, the drug has direct trichomonacidal and amebacidal activity against Trichomonas vaginalis and Entamoeba histolytica, and is useful in combatting infections caused by those microbial parasites. **Metronidazole** has also been reported to be effective (via both oral and topical application) in **treating** skin disorders such as rosacea, ulcers infected with anaerobic bacteria, including decubitus ulcers (bed or pressure sores), venous ulcers, and diabetic foot ulcers, and other anaerobic infections such as post operative sepsis. There have also been reports that **metronidazole** is effective against perioral **dermatitis**

SUMM Rosacea, formerly called Acne rosacea, is a chronic skin disease primarily affecting adults, with recurring symptoms that include erythema, papules, pustules, rhinophyma, and telangiectses, primarily in the region of the nose, cheeks, and forehead. In rosacea, other acneform conditions, and certain types of **dermatitis**, topical **treatment** compositions are usually applied to both unafflicted and diseased areas. It is therefore desirable that a **treatment** have a mitigating effect on the diseased tissue and a prophylactic effect to prevent extension of involvement to the unafflicted tissue. Therefore, the preferred vehicles, and hence compositions, to obtain these desirable effects should contain **metronidazole** in a high thermodynamic activity and with a fast rate of release from the vehicle. Aqueous compositions of **metronidazole** would appear to meet the above criteria. However, the low solubility of **metronidazole** in water and several other solvents inhibits the preparation of an aqueous compositions. This has resulted in the development of oil-based, rather than aqueous, **metronidazole** compositions.

SUMM Thus, a need remains for **metronidazole**-containing dermatological preparations suitable for topical use which avoid the problems of current compositions. Such dermatological preparations would be useful for **treating** skin disorders such as rosacea and certain types of **dermatitis**, including perioral **dermatitis**. The present invention provides such preparations.

CLM What is claimed is:
15. A method for **treatment** of a human afflicted with a skin disorder which is a member of the group consisting of acne, rosacea, perioral **dermatitis** and seborrheic **dermatitis**, said method comprising topically applying to the afflicted skin region a therapeutically effective amount of a dermatological preparation in the form of an aqueous gel composition comprising: a therapeutically effective amount of **metronidazole** as the sole active ingredient; a gelled hydrophilic and water-dispersible polymer having free carboxylic groups which is a polyacrylic acid polymer having a molecular weight in the range of about 1,250,000 to about 4,000,000 daltons; and an aqueous solvent for said metronidazole.

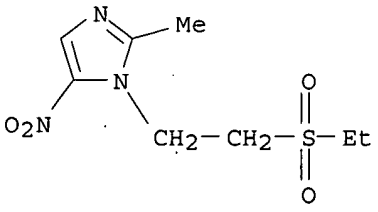
ACCESSION NUMBER: 89:45717 USPATFULL
TITLE: Topical metronidazole formulations and therapeutic uses thereof
INVENTOR(S): Borgman, Robert J., Mundelein, IL, United States

PATENT ASSIGNEE(S): Curatek Pharmaceuticals, Inc., Elk Grove Village, IL, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4837378		19890606
APPLICATION INFO.:	US 1988-144252		19880115 (7)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1986-819066, filed on 15 Jan 1986, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Schenkman, Leonard
LEGAL REPRESENTATIVE: Dressler, Goldsmith, Shore, Sutker & Milnamow, Ltd.
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 667
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 19387-91-8 REGISTRY
CN 1H-Imidazole, 1-[2-(ethylsulfonyl)ethyl]-2-methyl-5-nitro- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Imidazole, 1-[2-(ethylsulfonyl)ethyl]-2-methyl-5-nitro- (8CI)
OTHER NAMES:
CN 1-(Ethylsulfonylethyl)-2-methyl-5-nitroimidazole
CN Bioshik
CN CP 12574
CN Ethyl [2-(2-methyl-5-nitroimidazol-1-yl)ethyl] sulfone
CN Fasigin
CN Fasigyn
CN Glongyn
CN Pletil
CN Simplotan
CN Sorquetan
CN Tinidazol
CN **Tinidazole**
CN Tricolam
CN Trimonase
FS 3D CONCORD
MF C8 H13 N3 O4 S
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGPAT, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, NIOSHTIC, PHARMASEARCH, PROMT, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

661 REFERENCES IN FILE CA (1957 TO DATE)
5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
663 REFERENCES IN FILE CAPLUS (1957 TO DATE)

=>

L4 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2003 ACS
AN 1998:479396 CAPLUS
DN 129:100054
TI A nitroimidazole gel composition
IN Goodman, Michael; Lindahl, Ake
PA Bioglan Ireland (R & D) Ltd., Ire.
SO PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K009-00
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9827960	A2	19980702	WO 1997-GB3512	19971219
	WO 9827960	A3	19980911		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9853308	A1	19980717	AU 1998-53308	19971219
	AU 730812	B2	20010315		
	ZA 9711455	A	19980902	ZA 1997-11455	19971219
	EP 946143	A2	19991006	EP 1997-950300	19971219
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI				
	NZ 336258	A	20010427	NZ 1997-336258	19971219
	JP 2001507018	T2	20010529	JP 1998-528544	19971219
	NO 9902980	A	19990816	NO 1999-2980	19990617
	US 6348203	B1	20020219	US 2000-331367	20000616
PRAI	GB 1996-26513	A	19961220		
	WO 1997-GB3512	W	19971219		

AB A viscous hydrogel compn. for topical treatment of a **skin** condition involving dry or inflamed **skin**, comprises an antimicrobial nitroimidazole drug, a water miscible alkylene glycol, a hydroxyalkyl cellulose gelling agent and water, buffered to have a physiol. acceptable pH. Thus, a gel contained metronidazole 0.75, hydroxyethyl cellulose 1.8, propylene glycol 1.8, propylene glycol 5.0, Me p-hydroxybenzoate 0.15, Pr p-hydroxybenzoate 0.05, citric acid and sodium citrate qs to pH 5.5, and water to 100%.
ST nitroimidazole gel alkylene glycol cellulose
IT **Skin**, disease
(dry; nitroimidazole gel compn.)
IT Drug delivery systems
(gels, topical; nitroimidazole gel compn.)
IT Buffers
Dermatitis
Eczema
Skin
Viscosity
(nitroimidazole gel compn.)
IT Glycols, biological studies
Polysaccharides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitroimidazole gel compn.)
IT **Skin**, disease
(rosacea; nitroimidazole gel compn.)
IT 443-48-1, Metronidazole

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitroimidazole gel compn.)

IT 56-81-5, 1,2,3-Propanetriol, biological studies 57-55-6, 1,2-Propanediol, biological studies 64-19-7, Acetic acid, biological studies 68-04-2, Sodium citrate 71-50-1, Acetate, biological studies 107-41-5 107-88-0, Butylene glycol 111-29-5, Pentylene glycol 126-44-3, Citrate, biological studies 9004-34-6D, Cellulose, esters or ethers, biological studies 9004-62-0, Hydroxyethyl cellulose 9004-64-2, Hydroxypropyl cellulose 9005-25-8D, Starch, derivs., biological studies 14265-44-2, Phosphate, biological studies **19387-91-8**, Tinidazole 25265-71-8, Dipropylene glycol 36877-68-6D, Nitroimidazole, derivs. 37353-59-6, Hydroxymethyl cellulose
RL: THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(nitroimidazole gel compn.)

L4 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2003 ACS
AN 1998:629274 CAPLUS
DN 130:71392
TI Effect of azone on penetrating absorption of tinidazole
AU Chen, Shuping; Chen, Shihu; Zhao, Runding; Mao, Youhua
CS The People's Hospital of Shanxi Province, Xi'an, 710068, Peop. Rep. China
SO Zhongguo Yiyuan Yaoxue Zazhi (1998), 18(7), 295-298
CODEN: ZYYAEP; ISSN: 1001-5213
PB Zhongguo Yiyuan Yaoxue Zazhi Bianji Weiyuanhui
DT Journal
LA Chinese
CC 63-5 (Pharmaceuticals)
AB The penetrating absorption of tinidazole in mice **skin** apart from the body was studied, and effects of different concns. of tinidazole and azone on penetration absorption of tinidazole were compared. The amt. of absorption of tinidazole was obviously enhanced by increasing concn. of tinidazole and azone, and the basis for clin. pharmacy and prepn. of medicines for **skin** on selection of proper d. of tinidazole and azone were established.
ST tinidazole azone **skin** penetration absorption
IT **Skin**
(azone effect on penetration absorption of tinidazole)
IT **19387-91-8**, Tinidazole
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); **USES (Uses)**
(azone effect on penetration absorption of tinidazole)
IT 59227-89-3, Azone
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(azone effect on penetration absorption of tinidazole)

on with medicaments useful for **treating** wounds such as immunostimulating agents (Betafectin.TM.), antiviral agents, antikeratolytic agents, anti-inflammatory agents, antifungal agents, tretinoin, sunscreen agents, **dermatological** agents, topical antihistamine agents, antibacterial agents, bioadhesive agents, respiratory bursting inhibitors (lactic acid, adenosine), inhibitors of prostaglandin synthesis (ibuprofen, aspirin, indomethacin, meclofenomic acid, retinoic acid, padimate O, meclomen, oxybenzone), steroidal anti-inflammatory agents (corticosteroids including synthetic analogs), antimicrobial agents (neosporin ointment, silvadine), antiseptic agents, anesthetic agents (pramoxine hydrochloride, lidocaine, benzocaine), cell nutrient media, burn relief medications, sun burn medications, acne preparations, insect bite and sting medications, wound cleansers, wound dressings, scar reducing agents (vitamin E), and the like, and mixtures thereof, to further enhance the proliferation and resuscitation rate of mammalian cells. Preferably, the medicament useful for **treating** wounds is selected from the group consisting of immunostimulating agents, antiviral agents, antikeratolytic agents, anti-inflammatory agents, antifungal agents, tretinoin, sunscreen agents, **dermatological** agents, topical antihistamine agents, antibacterial agents, bioadhesive agents, respiratory bursting inhibitors, inhibitors of prostaglandin synthesis, antimicrobial agents, cell nutrient media, scar reducing agents, and mixtures thereof. More preferably, the medicament useful for **treating** wounds is selected from the group consisting of immunostimulating agents, antiviral agents, antikeratolytic agents, anti-inflammatory agents, antifungal agents, acne **treating** agents, sunscreen agents, **dermatological** agents, antihistamine agents, antibacterial agents, bioadhesive agents, and mixtures thereof.

DETD (B) a medicament useful for **treating** wounds.

DETD The present invention extends to methods for making the augmented cytoprotective-wound healing compositions. In general, the augmented compositions are made by admixing the therapeutic cytoprotective-wound healing composition with the medicament useful for **treating** wounds to prepare the augmented cytoprotective-wound healing composition.

DETD The present invention also extends to methods for employing the augmented cytoprotective-wound healing compositions. In a first aspect of this embodiment, the wound healing compositions of the present invention may be administered to cells concurrently with the cytotoxic agent and the medicament useful for **treating** wounds. In a second aspect of this embodiment, the wound healing compositions of the present invention and the medicament useful for **treating** wounds may be administered to cells prior to the administration of an anticancer cytotoxic agent to selectively protect non-cancerous cells in the presence of cancerous cells against the anticancer agent.

DETD (3) a medicament useful for **treating** wounds;

DETD (3) a medicament useful for **treating** wounds;

DETD (C) providing a medicament useful for **treating** wounds in an immediate release form; and

DETD (D) administering the anticancer cytotoxic agent from step (A), the wound healing composition from step (B) and the medicament useful for **treating** wounds from step (C) concurrently to mammalian cells to selectively protect non-cancerous mammalian cells in the presence of cancerous mammalian cells from the anticancer cytotoxic agent;

DETD wherein the wound healing composition and the medicament useful for **treating** wounds are released substantially immediately and the anticancer cytotoxic agent is released alter a period of time sufficient such that the cancerous cells have substantially metabolized the wound healing composition and the non-cancerous cells have not substantially metabolized the wound healing composition.

DETD (B) administering to mammalian cells a medicament useful for **treating** wounds;

DETD (C) waiting a period of time sufficient such that the cancerous cells

have substantially metabolized the wound healing composition and the medicament useful for **treating** wounds and the non-cancerous cells have not substantially metabolized the wound healing composition and the medicament useful for **treating** wounds; and

DETD (D) administering an anticancer cytotoxic agent to the mammalian cells to **treat** the cancerous cells which are unprotected by the wound healing composition and the medicament useful for **treating** wounds and the non-cancerous cells which are protected by the wound healing composition and the medicament useful for **treating** wounds to thereby increase the therapeutic effect of the anticancer cytotoxic agent.

DETD Window of susceptibility studies were conducted to determine the optimal **treatment** time of the cells with the cytoprotective agents prior to **treatment** of the cells with the cytotoxic agent. The normal cells and U937 leukemic tumor cells were pretreated separately in "wash out" studies with the single agents alone, and in combination, at the optimal concentration described above for various time periods, washed with fresh medium to remove the agents, and **treated** with the cytotoxic agent. The co-culture of normal and U937 leukemic tumor cells was **treated** essentially in the same manner except that the cells were not **treated** separately, but co-cultured. The optimal pretreatment time of the cells with the cytoprotective agents was found to be 24 hours prior to **treatment** of the cells with Doxorubicin. The cells were then placed in culture medium without the protective agents. The length of time that the cytoprotection lasted was 24 hours following Doxorubicin **treatment**. At this time, peripheral cell viability is a limiting factor because these cells are normal cells and do not remain in culture for extended periods of time.

DETD The cells were isolated and examined for morphological evidence of cytotoxicity or prevention of cytotoxicity. These studies determined the cytoprotective effect of the single agents and the combination of agents on the normal and tumor cells. DNA synthesis studies using 3H-thymidine (1 uCi/well) were carried out 4 hours prior to termination of the experiment to determine the effect of the formulations on the proliferation of the cells as a measure of the prevention of cytotoxicity and the extent of Doxorubicin-induced cytotoxicity. Propidium iodide exclusion analysis was carried out for direct quantitation of the cytotoxicity and the prevention of cytotoxicity. Each set of studies was performed in triplicate so that statistical analysis of the significant differences between the **treatment** groups could be conducted.

DETD Wash-out studies were conducted to determine viability of the peripheral blood monocytes co-cultured with U937 monocytic leukemia cells after 24 hour pretreatment of the cells with the cytoprotective agents followed by administration of Doxorubicin. With no Doxorubicin **treatment**, the viability of the control normal peripheral cells was enhanced from 55% to 68% with the use of 5 mM sodium pyruvate and 0.5% fatty acids, see FIG. 17. With no Doxorubicin **treatment**, the viability of the control U937 cells was enhanced from 43% to 62% with the use of the combination of the cytoprotective composition, 5 mM sodium pyruvate, 10 U Vitamin E, and 0.5% fatty acids, see FIG. 17.

DETD The viability of cultured peripheral monocytes without Doxorubicin was 66% and increased to 75% with the cytoprotective combination of 5 mM sodium pyruvate, 10 U Vitamin E, and 0.5% fatty acids, see FIG. 27. The viability of cultured peripheral monocytes **treated** with 0.5 ug/ml Doxorubicin was 47% and increased to 63.5% when pretreated with the cytoprotective combination of 5 mM sodium pyruvate, 10 U Vitamin E, and 0.5% fatty acids, see FIG. 27. The viability of cultured peripheral monocytes **treated** with 1 ug/ml Doxorubicin was 42% and increased to 66% when pretreated with the cytoprotective combination of 5 mM sodium pyruvate, 10 U Vitamin E, and 0.5% fatty acids, see FIGS. 27A-27B.

DETD The viability of cultured U937 tumor cells without Doxorubicin was 67% and did not increase when **treated** with any of the agents, see

FIG. 27. The viability of cultured U937 tumor cells with 0.5 ug/ml Doxorubicin **treatment** was 47% and the highest increase in viability occurred with pretreatment of 50 U Vitamin E and 0.5% fatty acids, see FIG. 26. The viability of cultured U937 tumor cells with 1 ug/ml Doxorubicin **treatment** was 45% and the highest increase in viability occurred with pretreatment of 10 U Vitamin E and 0.5% fatty acids, see FIGS. 26A-26B.

DETD Peripheral blood monocytes were exposed to 0.5 .mu.g/ml Adriamycin.TM. and **treated** wth wound healing composition components (Sodium Pyruvate, Vitamin E, and Fatty Acids) to determine their effect on cellular viability. Adriamycin.TM., an anthracycline antibiotic is cytotoxic to cells. Adriamycin.TM. decreases cellular viability and produces cellular death. The wound healing composition components were tested individually and in combination to determine if they could reverse cellular damage caused by Adriamycin.TM. and increase cellular vitality. Measurements were made using .sup.3 H-thymidine radioisotopic incorporation, which is a measure of DNA synthesis, i.e., cellular viability. The measure of cellular viability is the presence of living cells in the sample after **treatment**.

DETD

Results

1	2	3	4
	0.5 .mu.g/ml Adriamycin .TM.	0.5 .mu.g/ml Adriamycin .TM.	
Treatment Groups	**Treatment** - Percent Viability of Controls	**Treatment** - Percent Viability of Cells with Wound Healing Components	Difference in Cellular Viability
1 - Control	54	54	0
2 - Fatty Acids (0.5%)	54	47	-7
3 - Vitamin E (10 units)	53	50	-3
4 - Sodium Pyruvate (5 mm)	54	55	+1
5 - Pyruvate & Fatty Acids	54	55	+1
6 - Vitamin E & Fatty Acids	54	64	+10
7 - Pyruvate & Vitamin E	55	68	+13
8 - Pyruvate & Vitamin E & Fatty Acids (wound healing composition)	47	64	+17

Column 1 shows the different **treatment** groups.
Column 2 shows the percent of living cells (viability) present when the monocytes are **treated** with the cytotoxic agent, Adriamycin .TM..
Column 3 shows the viability of cells **treated** with Adriamycin .TM. and th
treatment.

Column 4 shows the change in viability from control due to the **treatment**.

DETD As set out in FIG. 50, razor cartridge 10 is typical of the type of shaving device to which the present invention is applicable in affording a wound healing composition delivery system which may be applied directly to the **skin** continuously with each stroke of the razor during the act of wet shaving. Razor cartridge 10 comprises a blade seat 12 having formed thereon a guard bar 14 for smoothing the **skin** adjacent to the cutting edge 16 of a razor blade 18 during shaving. Blade seat 12 further includes a channel 20 which may be used to load cartridge 10 upon a conventional reusable razor main frame (not shown) in the customary manner of sliding a receiving portion of the main frame into channel 20 or sliding channel 20 over the receiving portion of the razor main frame. Completing the main supporting structure of razor cartridge 10 and holding blade 18 in place against seat 12 is cap 22. While cartridge 10 has been illustrated as being of the single-blade type, it should be understood that this structure is shown for purposes of illustration only and that the invention to be described in detail herein is applicable not only to single-blade cartridges but equally as well to multiple-blade shaving cartridges. The basic components of cartridge 10 are fused, cemented, or otherwise bonded together and are commonly referred to in the trade as bonded razor blade cartridges. In the embodiment of the invention illustrated in FIG. 50, a strip 24 formed of an integral wound healing composition delivery system is cemented to cap 22 preferably within a recess 26 provided therefor. Strip 24 is disposed in juxtaposition with edge 16 of blade 18 and extended from a point adjacent one end of the blade to a point similarly adjacent to the opposite end of the blade. Strip 24 may be a continuous solid strip or a discontinuous strip comprising dots, or the like.

DETD A. A lubricating agent for reducing the frictional forces between the razor and the **skin**, e.g., a microencapsulated silicone oil.

DETD D. A cleaning agent which allows the whisker and **skin** debris to be washed more easily from the razor parts during shaving, e.g., a silicon polyethylene oxide block copolymer and detergent such as sodium lauryl sulfate.

DETD E. A medicinal agent for killing bacteria or repairing **skin** damage and abrasions.

DETD F. A cosmetic agent for softening, smoothing, conditioning, or improving the **skin**.

DETD In one preferred embodiment, the cross-linked polymethacrylate copolymer is POLYTRAP 6603 Polymer Powder, available from Dow Corning Corporation. POLYTRAP 6603 is a highly cross-linked polymethacrylate copolymer (acrylates copolymer) with high and selective oil adsorption capacity and hydrophobic surface properties. POLYTRAP 6603 Polymer Powder is capable of quickly adsorbing high levels of lipophilic materials while maintaining free-flowing powder characteristics. The adsorption of these lipophilic materials is a physical phenomenon controlled by the surface tension of the fluids on the polymer powder surface and filling of the interstitial voids by capillary action. This adsorption characteristic can be used to control the delivery of a fluid (converting liquids to solids) or to adsorb a liquid from a surface. Lipophilic materials are delivered by mechanical disruption of the agglomerate or vapor pressure differentials between the inside of the matrix and the outer environment surrounding the polymer. When rubbed on the **skin**, the lipophilic materials come into direct contact with the **skin** and meter out as the lipophilic materials is removed from the surface of the particle.

DETD In another preferred embodiment, the cross-linked polymethacrylate copolymer is MICRO SPONGE **SKIN** OIL ADSORBER 5640 POWDER, available from Dow Corning Corporation. MICROSPONGE **SKIN** OIL ADSORBER 5640 is a highly cross-linked polymethacrylate copolymer (acrylates copolymer) with selective oil and water adsorption capacity

hydrophilic/hydrophobic surface properties. MICROSPONGE **SKIN** OIL ADSORBER 5640 is capable of adsorbing high levels of lipophilic materials.

DETD In all cases, upon contact with the wet **skin** or by wetting of the razor cartridge, the wound healing composition delivery system becomes immediately and repeatedly applied to the **skin** with each stroke of the razor. Thus, its intended function is performed continuously throughout the shaving act as opposed to the requirement of pre-shave or after-shave **treatment**.

DETD The present invention extends to methods for employing the therapeutic razor cartridges comprising wound healing compositions. In general, a razor cartridge is employed by contacting the cartridge with **skin** during the process of shaving.

DETD (c) a mixture of saturated and unsaturated fatty acids wherein the fatty acids are those fatty acids required for the repair of cellular membranes and resuscitation of mammalian cells; and contacting the cartridge with **skin** during the process of shaving.

DETD In another aspect of Embodiment Four, the therapeutic razor cartridges comprising wound healing compositions (I.A-D, F+R) of the present invention may be combined with medicaments useful for **treating** wounds (M) to form razor cartridges comprising augmented wound healing compositions (I.A-D, F+R+M). In this embodiment, the combination of the razor cartridges comprising a wound healing composition of the present invention and the medicament useful for **treating** wounds provides an augmented razor cartridge comprising a wound healing composition having an enhanced ability to increase the proliferation and resuscitation rate of mammalian cells. For example, the therapeutic compositions of the present invention may be used in combination with medicaments useful for **treating** wounds such as immunostimulating agents (Betafectin.TM.), antiviral agents, antikeratolytic agents, anti-inflammatory agents, antifungal agents, tretinoin, sunscreen agents, **dermatological** agents, topical antihistamine agents, antibacterial agents, bioadhesive agents, respiratory bursting inhibitors (lactic acid, adenosine), inhibitors of prostaglandin synthesis (ibuprofen, aspirin, indomethacin, meclofenomic acid, retinoic acid, padimate O, meclomen, oxybenzone), steroidal anti-inflammatory agents (corticosteroids including synthetic analogs), antimicrobial agents (neosporin ointment, silvadine), antiseptic agents, anesthetic agents (pramoxine hydrochloride, lidocaine, benzocaine), cell nutrient media, burn relief medications, sun burn medications, acne preparations, insect bite and sting medications, wound cleansers, wound dressings, scar reducing agents (vitamin E), and the like, and mixtures thereof, to further enhance the proliferation and resuscitation rate of mammalian cells. Preferably, the medicament useful for **treating** wounds is selected from the group consisting of immunostimulating agents, antiviral agents, antikeratolytic agents, anti-inflammatory agents, antifungal agents, tretinoin, sunscreen agents, **dermatological** agents, topical antihistamine agents, antibacterial agents, bioadhesive agents, respiratory bursting inhibitors, inhibitors of prostaglandin synthesis, antimicrobial agents, cell nutrient media, scar reducing agents, and mixtures thereof. More preferably, the medicament useful for **treating** wounds is selected from the group consisting of immunostimulating agents, antiviral agents, antikeratolytic agents, anti-inflammatory agents, antifungal agents, acne **treating** agents, sunscreen agents, **dermatological** agents, antihistamine agents, antibacterial agents, bioadhesive agents, and mixtures thereof.

DETD (d) a medicament useful for **treating** wounds.

DETD The present invention extends to methods for making the razor cartridges comprising an augmented wound healing composition. In general, the razor cartridges comprising an augmented wound healing composition are made by affixing to the razor cartridge a wound healing composition and a medicament useful for **treating** wounds to prepare the augmented razor cartridges.

DETD The present invention extends to methods for employing the therapeutic razor cartridges comprising augmented wound healing compositions. In general, a razor cartridge is employed by contacting the augmented cartridge with **skin** during the process of shaving. In a preferred embodiment, the invention is directed to a method for employing a disposable razor cartridge comprising an augmented wound healing composition which comprises providing a cartridge comprising:

DETD (d) providing a medicament useful for **treating** wounds; and contacting the cartridge with **skin** during the process of shaving.

CLM What is claimed is:

14. An augmented wound healing composition having an enhanced ability to prevent and reduce injury to mammalian cells which comprises: (A) a therapeutic wound healing composition which comprises: (a) pyruvate selected from the group consisting of pyruvic acid, pharmaceutically acceptable salts of pyruvic acid, and mixtures thereof; (b) an antioxidant; and (c) a mixture of saturated and unsaturated fatty acids wherein the fatty acids are those fatty acids required for the repair of cellular membranes and resuscitation of mammalian cells; wherein components a, b, and c are present in amounts sufficient to synergistically enhance wound healing; and, (B) a medicament useful for **treating** wounds.

15. The augmented wound healing composition according to claim 14, wherein the medicament is selected from the group consisting of immunostimulating agents, antiviral agents, antikeratolytic agents, anti-inflammatory agents, antifungal agents, acne **treating** agents, sunscreen agents, **dermatological** agents, antihistamine agents, antibacterial agents, bioadhesive agents, respiratory bursting inhibitors, inhibitors of prostaglandin synthesis, antimicrobial agents, antiseptic agents, anesthetic agents, cell nutrient media, burn relief medications, sun burn medications, insect bite and sting medications, wound cleansers, wound dressings, scar reducing agents, and mixtures thereof.

16. A method for healing a wound in a mammal with an augmented wound healing composition which comprises administering to a mammal in need thereof: an augmented wound healing composition which comprises: (1) a therapeutic wound healing composition which comprises: (a) pyruvate selected from the group consisting of pyruvic acid, pharmaceutically acceptable salts of pyruvic acid, and mixtures thereof; (b) an antioxidant; and (c) a mixture of saturated and unsaturated fatty acids wherein the fatty acids are those fatty acids required for the repair of cellular membranes and resuscitation of mammalian cells; wherein components a, b, and c are present in amounts sufficient to synergistically enhance wound healing; and, (2) a medicament useful for **treating** wounds.

ACCESSION NUMBER: 97:66160 USPATFULL

TITLE: Therapeutic-wound healing compositions and methods for preparing and using same

INVENTOR(S): Martin, Alain, 31 Country Club Dr., Ringoes, NJ, United States 08551

	NUMBER	KIND	DATE
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APPLICATION INFO.:	US 1995-445813		19950522 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1994-187435, filed on 27 Jan 1994, now abandoned which is a continuation of Ser. No. US 1991-798392, filed on 26 Nov 1991, now abandoned which is a continuation-in-part of Ser. No. US 1991-663500, filed on 1 Mar 1991, now abandoned

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LEGAL REPRESENTATIVE:	Barish, Jean B.
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SUMM Many valuable anti-**inflammatory** steroids have been developed by various modifications of the basic steroid structure. For example, the introduction of a double bond at the 1,2 position into hydrocortisone increases glucocorticoid activity by approximately 4 orders of magnitude while at the same time reducing mineralocorticoid effects. Prednisone and prednisolone are examples of such a modification.

SUMM A second class of anti-**inflammatory** agents which are especially useful in the compositions of the present invention are the non-steroidal anti-**inflammatory** agents. The variety of compounds encompassed by this group are well-known to those skilled in the art. It is thought that these drugs act, at least in part, by the inhibition of prostaglandin synthetase. For detailed disclosure of the chemical structure, synthesis, side effects, etc., of non-steroidal anti-**inflammatory** agents, reference may be had to standard texts, including Anti-**inflammatory** Agents, Chemistry and Pharmacology, 1, R. A. Scherrer, et al., Academic Press, New York (1974), incorporated herein by reference.

SUMM Specific non-steroidal anti-**inflammatory** agents useful in the composition of the present invention include compounds of the the formula ##STR2## wherein R.sup.19 is --CH.sub.3 O, (--CH.sub.3).sub.2 N, --F or --CH.sub.3 ; R.sup.20 and R.sup.21 are --H or --CH.sub.3, R.sup.22 is --H, --CH.sub.3, --COOC.sub.2 H.sub.5, --CH.sub.2 CHOHCH.sub.2 OH, or --CH.sub.2 OCOCH.sub.3, M is --H, alkali metal or C.sub.1 -C.sub.20 alkyl, alkenyl, or aryl, Z is a halogen, CF.sub.3 or CH.sub.3 S; and G is .dbd.O or (--H).sub.2. The foregoing include, without limitation, salicylic acid, acetyl salicylic acid, methyl salicylate, glycol salicylate, salicylmides, benzyl-2,5-diacetoxybenzoic acid, ibuprofen, fulindac, naproxen, ketoprofen, etofenamate, phenylbutazone, and indomethacin. Mixtures of these non-steroidal anti-**inflammatory** agents may also be employed, as well as the pharmaceutically-acceptable salts and esters of these agents. Piroxicam is also useful.

SUMM Non-steroidal anti-**inflammatory** agents are preferably present in the compositions of the present invention at levels of about 0.05% to about 10%, by weight of the composition. They are more preferably present at levels of about 0.25% to about 5%, and are most preferably present at levels of about 1% to about 5%, by weight of the composition.

SUMM Other analgesic, antipyretic and anti-**inflammatory** agents useful in the compositions of the present invention can be found in Goodman, et al., The Pharmacological Basis of Therapeutics, 5th Ed., pp. 325-358, Macmillan Publishing Company, New York, (1975); and Wolfe, Burger's Medicinal Chemistry, 3, 4th Ed., John Wiley and Sons, New York, N.Y., pp. 1273-1316 (1981); both are incorporated herein by reference.

SUMM The antibacterials useful in the compositions and methods of the present invention include, without limitation, the chlorophors (chlorine releasing agents), phenols, substituted phenols, bisphenols, salicylanilides, hydroxy benzoic acids, polyhydric phenols, hydroxy quinolines, nitroheterocycles, e.g., nitrofurans and **nitroimidazoles**, nalidixic acid, oxolinic acid, quinoxaline- and phenazine-di-N-oxides, iodinin, cotrimoxazole, methanamine, B-lactam antibiotics such as the penicillins, cephalosporins, cephamycins, thienamycins, and clavulanic acid, nocardicins such as cephalothin and cefoxitin, non-lactam antibiotics such as the actinomycin group, bacitracin, tyrothricin, polymyxin and colistin, antibiotic polypeptides with a lactone ring such as etamycin and viridogrisein, staphylomycin, ostreogrycin, doricin, vernamycin, cycloheptamycin, telomycin, rufomycin A, ilamycin, streptogramime, mikamycin, gramicidin, albomycin,

bacteriocin, the colicins, edeine, phytoactin, valinomycin, viomycin, the antimycins, distamycin A, neotropsin, thiostrepton, polyene antifungal antibiotics such as nystatin, pimaricin, lucensomycin, rimocidin, amphotericin B, primycin, levorins A and B, candidin, lagosin, filipin, chainim, mycoticin, and flavofungin, macrolide antibiotics such as methymycin, picromycin, lancamycin, oleandomycin, erythromycin, carbomycin, the spiramycins, chalcomycin, borrelidin, tylosin, angolamycin, nonactin, the oligomycins, and maridomycin, aminoglycoside antibiotics such as streptomycin, kanamycin, paromomycin, neomycin, and gentamicin, the tetracyclines, the **steroidal** antibiotics, the ansamycins such as rifamycin, the streptovaricins, and geldamycin, the glutarimids such as cycloheximide or actidione, naramycin B, antitumor E-73, the streptovitacins, nucleoside antibiotics such as puromycin, tubercidin, angustmycin and psicofurarine, cordycepin, blasticidin, gougerotin, the polyoxins, 3'-amino-3'-deoxyguanosine, nucleocidin, amicetin, sparsomycin; anthracycline antibiotics such as daunomycin, adriamycin, olivomycin, chromomycin and mithramycin, nogalamycin, leukaeomycin, steffimycin, carminomycin 1, the phenazines, quinoxaline antibiotics such as echinomycin, the triostins, ionophores such as polyetherin A, monensin, and the nonclassifiable antibiotics such as actinomycetin, actithiazic acid, althiomycin, anthramycin, azaserine, the bleomycins, boromycin, bruneomycin, carzinophilin, cellocidin, chloramphenicol, cycloserine, flavensomycin, fumagillin, griseofulvin, hadacidin, kanchanomycin, lincomycin, micrococcin, the mitomycins, porfiromycin, nalidixic acid, novobiocin, pactamycin, patulin, pluramycin, protoanemonin, pyrrolnitrin, sarkomycin, sibiromycin, the sideromycins, tenuazonic acid, trichothecin, usnic acid, vancomycin and variotin.

SUMM The antiarthritics useful in the compositions of the present invention include, without limitation, the steroid and nonsteroidal anti-**inflammatories** discussed above, the bone active agents discussed herein, and gold salts.

SUMM The compositions of the present invention may additionally contain other adjunct components conventionally found in pharmaceutical compositions, not recited above, at their art-established usage levels. Thus, for example, the compositions may contain two or more compatible pharmaceutically-active materials for combination therapy; antimicrobials, antipruritics, astringents, local anesthetics, or non-steroidal anti-**inflammatory** agents could be employed when the active initially selected for therapy is a steroid. They may also contain materials useful in physically formulating various dosage forms of the present invention, such as excipients, dyes, perfumes, fragrances, opacifiers, thickening agents, preservatives, anti-oxidants, gelling agents, surfactants and stabilizers. Such materials, when added, should not unduly interfere with the penetration enhancement of these compositions. Such formula modifications to improve cosmetic acceptability are well within the skill of workers in the cosmetic and dermatological arts and, by themselves, constitute no part of the present invention.

SUMM While the choice of any particular agent in the treatment of a specific condition may be dictated by such factors as cost, availability, safety, and the like, such a choice frequently represents the personal experience of the artisan which may or may not be reproduceable. Further, the availability of many actives with equivalent efficacy makes the choice of the "best" specific agent or active, or combination or agents or actives, difficult. However, the selection of an agent, or combination of agents, which can be effectively penetrated to manage any forseeable condition is well within the skill of the art, and the actual selection of such agents (other than the selection of a penetrable agent or active) plays no part of this invention. For example, when a steroid is incorporated into the compositions of the present invention and the

resulting composition is applied to an afflicted/application situs, this invention provides a method for treating and preventing nonendocrine immunologic or rheumatic diseases, such as rheumatoid arthritis, rheumatic fever, disseminated lupus erythematosus, hypersensitivity reactions, such as bronchial asthma, serum sickness, anaphylaxis, bee stings, angioneurotic edema, hay fever, hemolytic enemia, drug reactions and agranulcytosis. Incorporation of a steroid into the compositions of the present invention and application of the resulting composition to an application situs also provides a method for treating diseases of the liver such as chronic active hepatitis, as well as certain neurological conditions, such as cerebral edema or an increase in intracranial pressure. The incorporation of a steroid and application of the resulting composition to an application situs further provides a method for treating and preventing **inflammatory** conditions such as ulcerative colitis, dermatitis (atopic, eczematoid, exfoliative, stasis, nummular, contact, or seborrheic), pemfhigus, gout and other **inflammations** of skin or mucous membranes caused by chemical, thermal, mechanical or radiant agents. In addition, the present invention may be formulated and used with a steroid in a veterinary context, for example in the treatment of dermatological disorders characterized by **inflammation** and dry or exudative dermatitis, eczematous dermatitis, contact dermatitis, seborrheic dermatitis, and as an adjunct in the treatment of dermatitis due to parasitic infestation.

SUMM More specifically, in a preferred embodiment, a safe and effective amount of a pharmaceutically-active antiviral agent selected from the group consisting of idoxuridine, iodoueoxyuridine, or a 6- or 2,6-substituted purine, recited above, is incorporated into the compositions of the present invention and applied to the afflicted situs, and a method of treating the pain and **inflammation** associated with herpes simplex, herpes zoster, and herpes varicella infection, including labial and genital herpes, is provided. Another preferred embodiment encompasses incorporating a safe and effective amount of griseofulvin into the compositions of the present invention and a method of treating the pain and **inflammation** associated with infections of skin, hair or nails, is accordingly provided when the resulting composition is topically applied to the afflicted situs.

DETD Composition 1 is applied to a human afflicted with dermatitis at the afflicted situs at a rate of 5 mg of composition per square centimeter of skin three times daily for a period of 5 days. Complete elimination of **inflammation** is noted after 48 hours. Substantially similar results are obtained when the composition is replaced by Composition II, III, IV or V of Example 1.

CLM What is claimed is:

1. A penetration-enhancing pharmaceutical composition for topical application, comprising: (a) a safe and effective amount of a non-steroidal anti-**inflammatory** agent selected from the group consisting of salicylic acid, acetyl salicylic acid, methyl salicylate, glycol salicylate, salicylmides, benzyl-2,5-diacetoxybenzoic acid, ibuprofen, fulindac, naproxen, ketoprofen, etofenamate, phenylbutazone, indomethacin, piroxicam, and mixtures thereof; (b) 0% to about 80% by weight of a solvent selected from ethanol or 2-propanol; (c) 0% to about 80% by weight water; and (d) about 10% to about 99.9% by weight of a penetration-enhancing vehicle consisting essentially of (i) N-(2-hydroxyethyl)pyrrolidone, and (ii) a cell-envelope disordering compound selected from the group consisting of methyl laurate, oleic acid, oleyl alcohol, monoolein, myristyl alcohol, and mixtures thereof; wherein component (d)(i) and (d)(ii) are present in a ratio of (d)(i):(d)(ii) of about 1:5 to about 500:1 by weight.

11. A penetration-enhancing pharmaceutical composition for topical application, comprising: (a) about 0.01% to about 10%, by weight, of a non-steroidal anti-**inflammatory** agent selected from the group

consisting of salicylic acid, acetyl salicylic acid, methyl salicylate, glycol salicylate, salicylmides, benzyl-2,5-diacetoxybenzoic acid, ibuprofen, fulindac, naproxen, ketoprofen, etofenamate, phenylbutazone, indomethacin, piroxicam, and mixtures thereof; (b) 0% to about 80% by weight of a solvent selected from ethanol and 2-propanol; (c) 0% to about 80% by weight water; (d) about 10% to about 99.9% by weight of a penetration-enhancing vehicle consisting essentially of (i) N-(2-hydroxyethyl)pyrrolidone, and (ii) a cell-envelope disordering compound selected from the group consisting of methyl laurate, oleic acid, oleyl alcohol, monoolein, myristyl alcohol, and mixtures thereof; wherein component (d)(i) and (d)(ii) are present in a ratio of (d)(i):(d)(ii) of about 5:1 to about 100:1 by weight.

20. A composition according to claim 1 wherein the non-steroidal anti-**inflammatory** agent is present at a level of about 0.05% to about 10% by weight.

PI US 4537776 19850827

L7 ANSWER 33 OF 34 USPATFULL

TI Topical **treatment** of blepharitis

AB A method and composition for **treating** blepharitis or blepharoconjunctivitis comprises topical administration of a nitroimidazole compound, e.g. metronidazole in a suitable carrier directly to affected ocular tissues. The carrier can be an artificial tear solution or an ointment or water soluble gel base.

SUMM The present invention relates to the field of **treating** abnormal eye inflammation and more particularly to the topical **treatment** of inflammations and other dysfunctions of the eyelid and conjunctiva. The present invention is especially concerned with the **treatment** of blepharitis and blepharoconjunctivitis particularly associated with ocular rosacea.

SUMM Rosacea is a disease of the **skin** (acne rosacea) and eyes (ocular rosacea) of unknown etiology and a variety of manifestations. The clinical and pathological features of the eye disease are nonspecific, and the disease is widely underdiagnosed by ophthalmologists.

SUMM References which discuss ocular rosacea include: "Ocular Rosacea" by M. S. Jenkins et al, American Journal of Opthalmology, Vol. 88:618-622 (1979); "Blepharitis Associated With Acne Rosacea and Seborrheic **Dermatitis**" by J. P. McCulley et al, in Oculocutaneous Diseases, edited by J. P. Callen et al, Little, Brown & Company, International Ophthalmology Clinics, Spring 1985, Vol, 25, No. 1, pp. 159-172; and "Ocular Rosacea" by D. J. Browning et al, Survey of Ophthalmology, Vol. 31, No. 3, November-December 1986, pp. 145-158.

SUMM In the article by McCulley et al mentioned above, on pages 170-172, several **treatments** for blepharitis are disclosed. These **treatments** include: topical antibiotics; oral tetracycline; SSA neutralizers; exoenzymatic inhibitors; vitamin A analogs; and other means of affecting meibomian gland secretions.

SUMM In another prior art reference, Textbook of **Dermatology**, 4th Edition, A. Rook et al editors, Vol. 2, p. 2152, there is a disclosure that Demodectic blepharitis may be **treated** with bathing with boric acid or with benzalkonium.

SUMM In the article by Browning et al mentioned above, on p. 155, there is a disclosure that for **treatment** of ocular rosacea only tetracycline has been critically studied. In the same article, there is mentioned that metronidazole has been used for **treatment** of **skin** lesions of rosacea. However, the article does not teach the use of a nitromidazole compound (including metronidazole) with a suitable carrier for topical **treatment** of ocular tissues.

SUMM In another reference, namely "Topical Metronidazole Therapy For Rosacea", by P. A. Bleicher et al, Arch **Dermatol**., Vol. 123, May 1987, pp. 609-614, there is a disclosure that metronidazole can be used in a gel for **treatment** of rosacea of the **skin**. However, there is no disclosure that metronidazole can be used for ocular rosacea.

SUMM The prior art also teaches other **treatments** for eye inflammations using the direct application of a **treating** composition to the eye. For example, in U.S. Pat. No. 4,612,193 to Gordon et al, there is a disclosure that a blepharitic infection (not characterized as being caused by ocular rosacea) can cause a stye and that an ointment is provided to **treat** the stye. The ointment is based on yellow mercuric oxide, boric acid, and wheat germ oil.

SUMM In the book Diseases of the Cornea, 2nd Edition, by M. G. Grayson, C. Z. Mosby Company, 1983, pp. 119-209, there is a disclosure that blepharitis can be **treated** using antibiotic ointments containing antibiotics such as bacitracin, erythromycin, chloramphenicol, and tetracycline. Other active agents for **treating** blepharitis include Rifampin, a very dilute steroid such as 0.12%, prednisolone, and polysulfide.

SUMM The prior art **treatments** for eye inflammations have several disadvantages. For example, when tetracycline is taken orally it takes between two to three months to have a significant effect. Furthermore, tetracycline is plagued with side effects such as super infections, light sensitivity, cramp feelings of the user, contra-indication if the user is pregnant, and resultant feelings that are similar to those when a person has the flu. Therefore, it would be desirable to avoid the use of tetracycline for the **treatment** of eye inflammations (e.g. ocular rosacea and related conditions).

SUMM Another eye condition is known as dry eye which results from an abnormal difficiency of tear production. A discussion of dry eye is found in the article entitled "Tear Physiology and Dry Eyes" by F. J. Holly et al, Survey of Ophthalmology, Vol. 22, No. 2, September-October 1977, pp. 69-87. As disclosed in the Holly et al article, the primary **treatment** for dry eye is the use of artificial tears applied topically. Unfortunately, blepharitis is often misdiagnosed as dry eye. As a result, **treatment** with artificial tears is inadequate to cure the patient's problem. It would be desirable to provide a pharmaceutical composition that would **treat** the actual blepharitis in the instance where the condition was misdiagnosed as dry eye.

SUMM Another problem that has received attention in the ophthalmological literature lately is infection by a parasite known as Acanthamoeba hystolytica which particularly plagues users of contact lenses. A particularly devastating infection results from this parasite leaving the victim particularly susceptible to blindness in an infected eye. A presently used **treatment** for Acanthamoeba is a therapeutic agent known as brolene which is an over-the-counter British stye medication. Other known **treatments** for Acanthamoeba include antibiotics such as micadasol and mediasforan. However, it would be desirable if another nonantibiotic agent could be applied topically to alleviate the deleterious conditions caused by the Acanthamoeban organism.

SUMM Another problem associated with wearers of contact lenses is the formation of lumps under the lenses. Lumpy deposits formed under the contact lenses are very often due to undiagnosed blepharitis. By alleviating the underlying blepharitis condition, the cause of lump formation under contact lenses could be alleviated or removed. In this respect, it would be desirable to provide a **treatment** to prevent lump formation under contact lenses that result from undiagnosed blepharitis.

SUMM Although systemic **treatments** for eye conditions are known, such **treatments** are not popular with ophthalmologists. An eye doctor generally prefers to prescribe an eye medicine that is administered topically to the eye rather than prescribe a pill or the like which administers the medicine systemically. Therefore, it would be desirable to provide a **treatment** for blepharitis, or blepharoconjunctivitis, or ocular rosacea generally that is administered in a form such as a topically applied ointment or topically applied drops.

SUMM Accordingly, it is an object of the present invention to alleviate the

disadvantages and deficiencies of the prior art by providing a **treatment** for blepharitis, blepharoconjunctivitis, and ocular rosacea that is administered in the form of eye drops or other topically administered eye preparations.

SUMM Another object of the invention is to provide a **treatment** that avoids the use of tetracycline or other antibiotics for **treating** ocular inflammations such as ocular rosacea and related conditions.

SUMM Another object of the invention is to provide a pharmaceutical composition that **treats** actual blepharitis in an instance where the actual condition is misdiagnosed as dry eye.

SUMM Still another object of the invention is to provide a topical **treatment** for the eye conditions resulting from infection by Acanthamoeba hystolytica.

SUMM Yet another object of the invention is to provide a **treatment** to prevent lump formation under contact lenses that result from undiagnosed blepharitis.

SUMM In accordance with the teachings of the present invention, a pharmaceutical composition is provided for **treating** blepharitis and blepharoconjunctivitis generally and especially associated with ocular rosacea. The pharmaceutical composition of the invention includes an amount of a nitroimidazole compound effective for **treating** the blepharitis and/or blepharoconjunctivitis and/or ocular rosacea; and a carrier for the nitroimidazole compound wherein the carrier is suitable for direct application to the eye tissues. The nitroimidazole compound is selected from the group consisting of metronidazole, nimorazole, **tinidazole**, ordinidazole, secnidazole, and carnidazole. The preferred compound is metronidazole.

SUMM The composition of the invention is applied to ocular tissues directly for **treating** the conditions of blepharitis, blepharoconjunctivitis, and ocular rosacea.

DETD By employing the principles of the invention, numerous objects are realized and numerous benefits are obtained. For example, a pharmaceutical composition is provided to **treat** blepharitis, blepharcoconjunctivitis, and ocular rosacea and is administered in the form of an ointment or in the form of eye drops. The method of **treatment** of the invention avoids the use of tetracycline for **treating** ocular rosacea and related conditions. With the invention, a pharmaceutical composition is provided that **treats** actual blepharitis in the case where the condition is misdiaqnosed as dry eye. The invention provides a topical **treatment** for eye conditions resulting from infection by Acanthamoeba hystolytica. The invention provides a **treatment** to prevent lump formation under contact lenses that result from blepharitis.

CLM What is claimed is:

1. A pharmaceutical composition, comprising: an amount of metronidazole effective to **treat** blepharitis and blepharoconjunctivitis in an animal or human patient; and a carrier for said metronidazole compound, said carrier suitable for topical application to ocular tissues, wherein said carrier includes an artificial tear composition.

10. A method of **treating** a human being for blepharitis or blepharoconjunctivitis, which comprises: administering to said human being an amount of metronidazole applied directly to ocular tissues effective to **treat** the blepharitis or blepharoconjunctivitis.

11. A method of **treating** a human being for blepharitis or blepharoconjunctivitis which comprises: administering to said human

being an amount of a compound in the class of nitroimidazole compounds applied directly to ocular tissues effective to **treat** the blepharitis or blepharoconjunctivitis.

12. The method of **treating** blepharitis or blepharoconjunctivitis described in claim 11 wherein the nitroimidazole compound is selected from the group consisting of metronidazole, nimorazole, **tinidazole**, ordinidazole, secnidazole, and carnidazole.

13. The method of **treating** blepharitis or blepharoconjunctivitis described in claim 12 wherein the nitroimidazole compound is metronidazole in a range of 0.1-2% by weight.

IT 443-48-1 3366-95-8, Secnidazole 6506-37-2, Nimorazole 16773-42-5 **19387-91-8** 36877-68-6D, Nitroimidazole, derivs. 42116-76-7, Carnidazole
(blepharitis or blepharoconjuctivitis treatment with pharmaceutical contg.)

ACCESSION NUMBER: 90:73483 USPATFULL
TITLE: Topical **treatment** of blepharitis
INVENTOR(S): Martin, Neil F., Silver Spring, MD, United States
Robinson, Howard N., Lutherville, MD, United States
PATENT ASSIGNEE(S): Bloom, Leonard, Towson, MD, United States (part interest)
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	NUMBER	KIND	DATE	
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APPLICATION INFO.:	US 1988-204547		19880609	(7)
DOCUMENT TYPE:	Utility			